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

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4 **Title: Selenium and bone health: a protocol for a systematic review and meta-**
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6 **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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4 **Ethics and dissemination** Since no private and confidential patient data will be
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6 contained in the reporting, approval from an ethics committee is not required. The
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8 results will be published in a peer-reviewed journal. The study raises no ethical issues.
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11 **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.

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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4 development.⁹ Animal studies have shown that selenium-deprivation can retard
5
6 growth and change bone metabolism.¹⁰ Such effects are associated with reduced
7
8 BMD, impaired bone microarchitecture and increased bone resorption. Previous
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10 clinical studies have investigated the effects of selenium on bone health, however, the
11
12 results are inconclusive. Some suggested that serum and dietary selenium were
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14 positively correlated with BMD,^{11 12} while other showed that neither serum nor
15
16 dietary selenium was associated with osteoporosis.^{13 14} Meanwhile, some case-control
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18 studies revealed that the dietary intake of selenium was associated with reduced risk
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20 of osteoporotic hip fracture.^{15 16}
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30 Meta-analysis is an effective tool for revealing trends that may not be apparent,
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32 and it also helps in establishing clinical policies and guidelines. Thus, we aimed to
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34 systematically examine the existing literature on the associations between dietary or
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36 serum selenium concentrations and BMD, osteoporosis, or osteoporotic fractures, and
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38 to quantify such associations through meta-analysis where feasible.
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45 **METHODS**

46 **Study design**

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48 The aim of this meta-analysis is to investigate the associations between dietary intake
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50 or serum levels of selenium and BMD, osteoporosis, or osteoporotic fractures. This
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52 protocol was developed according to the Preferred Reporting Items for Systematic
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54 Review and Meta-Analyses Protocols (PRISMA-P) 2015 Statement,¹⁷ and has been
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4 registered in the international prospective register of systematic reviews PROSPERO
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6 network (registration number: CRD42019147188).
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10 11 **Eligibility criteria**

12 13 14 Types of studies

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16 The meta-analysis will include both interventional and observational studies, inclusive
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18 of case-control studies, randomized controlled trials, cross-sectional studies and
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20 cohort studies which focus on the associations between dietary intake or serum levels
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22 of selenium and BMD, osteoporosis, or osteoporotic fractures.
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30 31 Types of participants

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33 The participants in the included studies must be with information on dietary intake or
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35 serum levels of selenium, and with data of BMD or diagnosis of osteoporosis or
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37 osteoporotic fractures. No sex, ethnicity, economic status, geographical limitations, or
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39 education restrictions will be applied.
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45 46 Types of exposure/intervention

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48 Two main forms of exposure will be included, i.e., dietary intake selenium and serum
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50 levels of selenium.
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55 56 Types of outcome measures

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58 Primary outcomes will include BMD values and the prevalence or incidence of
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4 osteoporosis. The secondary outcome will be the prevalence or incidence of
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6 osteoporotic fractures. There will be no restriction on site and measuring method.
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10 11 **Information sources**

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14 Systematic literature searches will be undertaken across PubMed, Embase and
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17 Cochrane Library by applying the specified search strategy to identify relevant studies
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19 up to October 2019 on each platform or database. In addition, the references of the
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21 retrieved literature will be manually searched, and the relevant studies and systematic
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23 reviews will be scanned for additional eligible studies.
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30 31 **Search strategy**

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33 Keyword terms or medical subject heading terms (MESH) will be used to search for
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35 eligible studies in the databases mentioned above. The electronic search strategy is
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37 presented in **Table 1**. All the search terms will be adapted for different syntax rules of
38
39 the databases.
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46 47 **Study selection**

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49 The search results from the three electronic databases will be sent to Endnote. After
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51 removing duplicates, two investigators will be responsible for screening the titles and
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53 abstracts of all the retrieved literature to identify eligible studies. In case that the
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55 eligibility of a study cannot be determined, the full text will be reviewed for inclusion
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57 according to prespecified inclusion and exclusion criteria. There will be no restriction
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4 on the publication date and language. The study selection process will be summarized
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6 based on the PRISMA flow diagram. Disagreements between the two investigators
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8 will be resolved by discussing with a third investigator.
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11 12 13 14 **Data extraction**

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16 Two investigators will be engaged to independently extract the following data in a
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18 standardized collection form: publication information (author, year of publishing);
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20 study information (country of origin, study setting, data sources, study period);
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22 demographic information (sample size, age, and sex distribution); exposure
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24 information (dietary or serum selenium concentrations); outcome information (BMD,
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26 osteoporosis, osteoporotic fractures). Then, the effect sizes (mean difference [MD],
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28 odds ratio [OR], relative risk [RR], hazard ratio [HR] or beta coefficient [β]) will be
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30 either extracted directly or calculated based on the information in the original studies
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32 whenever possible. If the relevant data is not reported in an included study, the
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34 missing information will be obtained by contacting the authors directly as far as
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36 possible. The two investigators responsible for reviewing the literature will resolve
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38 any disagreements through discussions, and a third independent investigator may be
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40 involved into the discussion if required.
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53 **Assessment of risk of bias**

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55 The Cochrane risk of bias assessment tool will be used to assess the quality of
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57 RCTs,¹⁸ while the Newcastle-Ottawa Quality Scale (NOS) will be used to assess the
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4 quality of observational studies.¹⁹ Two investigators will be engaged to conduct the
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6 risk of bias assessment independently, and disagreements will be resolved through
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8 discussions.
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11 12 13 14 **Data analysis**

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16 Firstly, the characteristics of included studies will be summarized using baseline
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18 tables and narrative texts. The proposed study will calculate the MD, the pooled OR,
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20 RR, HR or β and the corresponding 95% CIs. Then, Cochrane's Q test and the I^2
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22 statistics will be used to assess the heterogeneity of the included studies, where p
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24 value > 0.05 of the Q statistics and I^2 value $< 50\%$ indicate statistical homogeneity. If
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26 the included studies are found to be statistically homogeneous, the fixed effects
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28 models will be used to pool the data during meta-analysis; otherwise, the random
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30 effects models will be used instead. Statistical analyses will be conducted in Review
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32 Manager-5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane
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34 Collaboration, 2014) and Stata-11.0 (StataCorp LP, College Station, TX) statistical
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36 software. Statistical significance is considered at p value < 0.05 .
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48 **Assessment of publication bias**

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50 If the number of included studies is greater than 10, a funnel plot will be constructed
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52 and the Egger test will be conducted to observe the publication bias. The existence of
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54 publication bias is confirmed when the funnel plot shows an asymmetric pattern.
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58 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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4 The health of the skeletal system is important for elderly people.¹ Nowadays,
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6 osteoporosis is becoming increasingly more prevalent with population aging around
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8 the world, presenting a severe public health problem in the future.⁵ Selenium is an
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10 essential element for bones, and plays an important role in skeletal development.¹⁰ An
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12 in-depth understanding of the relationship between selenium and bone health is useful
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14 for designing early life interventions. The sample size of previous studies might have
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16 not always been big enough to achieve sufficient statistical power, which could
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18 explain, at least in part, why the statistical difference in some instances was not
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20 reached, despite the obvious trends. Therefore, the aim of this systematic review and
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22 meta-analysis is to summarize the available evidence to investigate the associations
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24 between selenium and bone health. The results of this study will deepen the existing
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26 knowledge base on the pathogenesis of osteoporosis, and promote the development of
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28 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.

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Methodology: Jing Wu, Ziyang Wu, Hongyi He, Zidan 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 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]
3	1 AND 2

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			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

1 Registration

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4 [#2](#) If registered, provide the name of the registry (such as P4, P7-8
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9 Authors

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13 Contact [#3a](#) Provide name, institutional affiliation, e-mail address of all P1-2
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15 protocol authors; provide physical mailing address of
16
17 corresponding author
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20 Contribution [#3b](#) Describe contributions of protocol authors and identify the P14-15
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22 guarantor of the review
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25 Amendments

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29 [#4](#) If the protocol represents an amendment of a previously n/a
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48 Role of sponsor or [#5c](#) Describe roles of funder(s), sponsor(s), and / or institution(s), P14
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50 funder if any, in developing the protocol
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53 Introduction

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1		already known	
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4	Objectives	#7 Provide an explicit statement of the question(s) the review will	P8-9
5		address with reference to participants, interventions,	
6		comparators, and outcomes (PICO)	
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11	Methods		
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14	Eligibility criteria	#8 Specify the study characteristics (such as PICO, study design,	P8-9
15		setting, time frame) and report characteristics (such as years	
16		considered, language, publication status) to be used as	
17		criteria for eligibility for the review	
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24	Information	#9 Describe all intended information sources (such as electronic	P9
25		databases, contact with study authors, trial registers or other	
26	sources	grey literature sources) with planned dates of coverage	
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32	Search strategy	#10 Present draft of search strategy to be used for at least one	P18
33		electronic database, including planned limits, such that it	
34		could be repeated	
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39	Study records -	#11a Describe the mechanism(s) that will be used to manage	P10-11
40		records and data throughout the review	
41	data management		
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45	Study records -	#11b State the process that will be used for selecting studies (such	P9-10
46		as two independent reviewers) through each phase of the	
47	selection process	review (that is, screening, eligibility and inclusion in meta-	
48		analysis)	
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54	Study records -	#11c Describe planned method of extracting data from reports	P10
55		(such as piloting forms, done independently, in duplicate), any	
56	data collection		
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1	process		processes for obtaining and confirming data from investigators	
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4	Data items	#12	List and define all variables for which data will be sought	P10
5			(such as PICO items, funding sources), any pre-planned data	
6			assumptions and simplifications	
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11	Outcomes and	#13	List and define all outcomes for which data will be sought,	P8
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13	prioritization		including prioritization of main and additional outcomes, with	
14			rationale	
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18	Risk of bias in	#14	Describe anticipated methods for assessing risk of bias of	P10-11
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20	individual studies		individual studies, including whether this will be done at the	
21			outcome or study level, or both; state how this information will	
22			be used in data synthesis	
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28	Data synthesis	#15a	Describe criteria under which study data will be quantitatively	P10-11
29			synthesised	
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34	Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe	P11
35			planned summary measures, methods of handling data and	
36			methods of combining data from studies, including any	
37			planned exploration of consistency (such as I ² , Kendall's τ)	
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44	Data synthesis	#15c	Describe any proposed additional analyses (such as	n/a
45			sensitivity or subgroup analyses, meta-regression)	
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49	Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type	n/a
50			of summary planned	
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54	Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as	P11
55			publication bias across studies, selective reporting within	
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studies)

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4 Confidence in [#17](#) Describe how the strength of the body of evidence will be n/a
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6 cumulative assessed (such as GRADE)
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8 evidence
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BMJ Open

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

Journal:	<i>BMJ Open</i>
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Primary Subject Heading:	Nutrition and metabolism
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Keywords:	Bone diseases < ORTHOPAEDIC & TRAUMA SURGERY, PUBLIC HEALTH, Orthopaedic & trauma surgery < SURGERY

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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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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

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4 1 assessment tool will be used where appropriate.
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6 2 **Ethics and dissemination** Since no private and confidential patient data will be
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9 3 contained in the reporting, approval from an ethics committee is not required. The
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12 4 results will be published in a peer-reviewed journal. The study raises no ethical issues.
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14 5 **PROSPERO registration number** CRD42019147188
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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

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

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

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).

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.

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.

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.

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.

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.

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

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4 1 the databases.
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9 3 **Study selection**

10 4 The search results from the three electronic databases will be sent to Endnote. After
11
12 5 removing duplicates, two investigators will be responsible for screening the titles and
13
14 6 abstracts of all the retrieved literature to identify eligible studies. In case that the
15
16 7 eligibility of a study cannot be determined, the full text will be reviewed for inclusion
17
18 8 according to prespecified inclusion and exclusion criteria. There will be no restriction
19
20 9 on the publication date and language. The study selection process will be summarized
21
22 10 based on the PRISMA flow diagram. Disagreements between the two investigators
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24 11 will be resolved by discussing with a third investigator.
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35 13 **Data extraction**

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37 14 Two investigators will be engaged to independently extract the following data in a
38
39 15 standardized collection form: publication information (author, year of publishing);
40
41 16 study information (country of origin, study setting, data sources, study period);
42
43 17 demographic information (sample size, age, and sex distribution); exposure
44
45 18 information (dietary or serum selenium concentrations); outcome information (T-
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47 19 score , BMD values, the prevalence or incidence of osteoporosis or osteoporotic
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49 20 fractures). Then, both the adjusted and unadjusted effect sizes (mean difference [MD],
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51 21 odds ratio [OR], relative risk [RR], hazard ratio [HR] or beta coefficient [β]) will be
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53 22 either extracted directly or calculated based on the information in the original studies
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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

7 **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

14 **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

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

9 **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

15 **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

20 **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

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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.

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 the existing knowledge base on the pathogenesis of osteoporosis, and promote the
- 2 development of preventive or treatment strategies in this field.

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4 **1 COMPETING INTERESTS**

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6 2 The authors declare that they have no conflict of interest.
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12 **4 PATIENT CONSENT FOR PUBLICATION**

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14 5 Not required.
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55 21 Data curation: Jing Wu, Ziyang Wu, Hongyi He, Zidan Yang

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57 22 Methodology: Jing Wu, Ziyang Wu, Hongyi He, Zidan Yang
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- 2 Writing – review & editing: Yilun Wang and Tuo Yang

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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.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Reporting 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.

			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

1 Registration

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4 [#2](#) If registered, provide the name of the registry (such as P4, P7-8
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6 PROSPERO) and registration number
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9 Authors

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13 Contact [#3a](#) Provide name, institutional affiliation, e-mail address of all P1-2
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15 protocol authors; provide physical mailing address of
16
17 corresponding author
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20 Contribution [#3b](#) Describe contributions of protocol authors and identify the P14-15
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22 guarantor of the review
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25 Amendments

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29 [#4](#) If the protocol represents an amendment of a previously n/a
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31 completed or published protocol, identify as such and list
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33 changes; otherwise, state plan for documenting important
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35 protocol amendments
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38 Support

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42 Sources [#5a](#) Indicate sources of financial or other support for the review P14
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45 Sponsor [#5b](#) Provide name for the review funder and / or sponsor P14
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48 Role of sponsor or [#5c](#) Describe roles of funder(s), sponsor(s), and / or institution(s), P14
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50 funder if any, in developing the protocol
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53 Introduction

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56 Rationale [#6](#) Describe the rationale for the review in the context of what is P6-7
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1		already known	
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4	Objectives	#7 Provide an explicit statement of the question(s) the review will	P8-9
5		address with reference to participants, interventions,	
6		comparators, and outcomes (PICO)	
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11	Methods		
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14	Eligibility criteria	#8 Specify the study characteristics (such as PICO, study design,	P8-9
15		setting, time frame) and report characteristics (such as years	
16		considered, language, publication status) to be used as	
17		criteria for eligibility for the review	
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24	Information	#9 Describe all intended information sources (such as electronic	P9
25		databases, contact with study authors, trial registers or other	
26	sources	grey literature sources) with planned dates of coverage	
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32	Search strategy	#10 Present draft of search strategy to be used for at least one	P18
33		electronic database, including planned limits, such that it	
34		could be repeated	
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39	Study records -	#11a Describe the mechanism(s) that will be used to manage	P10-11
40		records and data throughout the review	
41	data management		
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45	Study records -	#11b State the process that will be used for selecting studies (such	P9-10
46		as two independent reviewers) through each phase of the	
47	selection process	review (that is, screening, eligibility and inclusion in meta-	
48		analysis)	
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54	Study records -	#11c Describe planned method of extracting data from reports	P10
55		(such as piloting forms, done independently, in duplicate), any	
56	data collection		
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1	process		processes for obtaining and confirming data from investigators	
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4	Data items	#12	List and define all variables for which data will be sought	P10
5			(such as PICO items, funding sources), any pre-planned data	
6			assumptions and simplifications	
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11	Outcomes and	#13	List and define all outcomes for which data will be sought,	P8
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13	prioritization		including prioritization of main and additional outcomes, with	
14			rationale	
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19	Risk of bias in	#14	Describe anticipated methods for assessing risk of bias of	P10-11
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21	individual studies		individual studies, including whether this will be done at the	
22			outcome or study level, or both; state how this information will	
23			be used in data synthesis	
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29	Data synthesis	#15a	Describe criteria under which study data will be quantitatively	P10-11
30			synthesised	
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34	Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe	P11
35			planned summary measures, methods of handling data and	
36			methods of combining data from studies, including any	
37			planned exploration of consistency (such as I ² , Kendall's τ)	
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44	Data synthesis	#15c	Describe any proposed additional analyses (such as	n/a
45			sensitivity or subgroup analyses, meta-regression)	
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49	Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type	n/a
50			of summary planned	
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54	Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as	P11
55			publication bias across studies, selective reporting within	
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studies)

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4 Confidence in [#17](#) Describe how the strength of the body of evidence will be n/a
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6 cumulative assessed (such as GRADE)
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8 evidence
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BMJ Open

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

Journal:	<i>BMJ Open</i>
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Secondary Subject Heading:	Public health
Keywords:	Bone diseases < ORTHOPAEDIC & TRAUMA SURGERY, PUBLIC HEALTH, Orthopaedic & trauma surgery < SURGERY

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4 1 **Title: Selenium and bone health: a protocol for a systematic review and meta-**
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6 2 **analysis**
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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

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4 1 assessment tool will be used where appropriate.
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6 2 **Ethics and dissemination** Since no private and confidential patient data will be
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9 3 contained in the reporting, approval from an ethics committee is not required. The
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11 4 results will be published in a peer-reviewed journal. The study raises no ethical issues.
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14 5 **PROSPERO registration number** CRD42019147188
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For peer review only

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

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

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

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).

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.

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.

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.

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 osteopenia 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 **Information sources**

15 Systematic literature searches will be undertaken across PubMed, Embase and
16 Cochrane Library by applying the specified search strategy to identify relevant studies
17 up to October 2019 on each platform or database. In addition, the references of the
18 retrieved literature will be manually searched. And Grey literature will also be
19 searched included study registries (e.g., ClinicalTrials.gov and google scholar). The
20 relevant studies and systematic reviews will be scanned for additional eligible studies.

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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 **Study selection**

7 The search results from the three electronic databases will be sent to Endnote. After
8 removing duplicates, two investigators will be responsible for screening the titles and
9 abstracts of all the retrieved literature to identify eligible studies. In case that the
10 eligibility of a study cannot be determined, the full text will be reviewed for inclusion
11 according to prespecified inclusion and exclusion criteria. There will be no restriction
12 on the publication date and language. The study selection process will be summarized
13 based on the PRISMA flow diagram. Disagreements between the two investigators
14 will be resolved by discussing with a third investigator.

15 **Data extraction**

16 Two investigators will be engaged to independently extract the following data in a
17 standardized collection form: publication information (author, year of publishing);
18 study information (country of origin, study setting, data sources, study period);
19 demographic information (sample size, age, and sex distribution); exposure
20 information (dietary or serum selenium concentrations); outcome information (T-

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.

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.

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

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.

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6 2 **Ethics and dissemination**

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9 3 As this meta-analysis will be performed based on published studies, and no private
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11 4 and confidential patient data will be contained in the reporting, approval from an
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13 5 ethics committee is not required. The results will be disseminated through publication
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15 6 in a peer- reviewed journal. The study raises no ethical issues.
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22 8 **DISCUSSION**

23
24 9 The health of the skeletal system is important for elderly people.¹ An in-depth
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26 10 understanding of the relationship between selenium and bone health is useful for
27
28 11 designing early life interventions. Selenoproteins expressed in human fetal osteoblasts
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30 12 would appear to protect the bone against oxidative stress, which may contribute to the
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32 13 development of osteoporosis by inhibiting osteoblastic differentiation of bone marrow
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34 14 stromal cells.^{26 27} The trace element selenium, as a critical constituent of
35
36 15 selenoproteins, is much more likely to be an essential role in the associations between
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38 16 selenium and bone mineral density. To our best knowledge, there are at least 10
39
40 17 studies that have investigated the associations between dietary or serum selenium
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42 18 concentrations and BMD, osteoporosis, or osteoporotic fractures. Of them, two
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44 19 studies suggested that serum and dietary selenium were likely to positively correlate
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46 20 with BMD,^{13 14} and three studies showed that dietary selenium was negatively
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48 21 associated with osteoporotic fractures.^{17 18 28} On the contrary, one study found no
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50 22 association between dietary selenium and BMD,²⁹ and four studies reported that
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4 1 neither serum nor dietary selenium was related to osteoporosis.^{15 16 30 31} Contradictory
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6 2 results of these studies might be related to the differences in study design and sample
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9 3 characteristics. So it's still controversial whether the contents of selenium can directly
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11 4 influence BMD and affect the pathogenesis of osteoporosis. The sample size of
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14 5 previous studies might have been too small to achieve sufficient statistical power,
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17 6 which could explain, at least in part, why the statistical difference in some instances
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20 7 was not reached, despite the obvious trends. Therefore, the aim of this systematic
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22 8 review and meta-analysis is to summarize the available evidence to investigate the
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25 9 associations between selenium and bone health. The results of this study will deepen
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28 10 the existing knowledge base on the pathogenesis of osteoporosis, and promote the
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31 11 development of preventive or treatment strategies in this field.
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4 **1 COMPETING INTERESTS**

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6 2 The authors declare that they have no conflict of interest.
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12 **4 PATIENT CONSENT FOR PUBLICATION**

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14 5 Not required.
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51 **19 AUTHOR'S CONTRIBUTIONS**

52
53 20 Conceptualization: Yilun Wang and Dongxing Xie

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55 21 Data curation: Jing Wu, Ziying Wu, Hongyi He, Zidan Yang

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57 22 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

For peer review only

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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]
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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.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Reporting 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.

			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

1 Registration

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4 [#2](#) If registered, provide the name of the registry (such as P4, P7-8
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6 PROSPERO) and registration number
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9 Authors

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13 Contact [#3a](#) Provide name, institutional affiliation, e-mail address of all P1-2
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15 protocol authors; provide physical mailing address of
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17 corresponding author
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20 Contribution [#3b](#) Describe contributions of protocol authors and identify the P14-15
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22 guarantor of the review
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25 Amendments

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29 [#4](#) If the protocol represents an amendment of a previously n/a
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31 completed or published protocol, identify as such and list
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33 changes; otherwise, state plan for documenting important
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35 protocol amendments
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38 Support

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42 Sources [#5a](#) Indicate sources of financial or other support for the review P14
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45 Sponsor [#5b](#) Provide name for the review funder and / or sponsor P14
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48 Role of sponsor or [#5c](#) Describe roles of funder(s), sponsor(s), and / or institution(s), P14
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50 funder if any, in developing the protocol
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53 Introduction

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56 Rationale [#6](#) Describe the rationale for the review in the context of what is P6-7
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1		already known	
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4	Objectives	#7 Provide an explicit statement of the question(s) the review will	P8-9
5		address with reference to participants, interventions,	
6		comparators, and outcomes (PICO)	
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11	Methods		
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14	Eligibility criteria	#8 Specify the study characteristics (such as PICO, study design,	P8-9
15		setting, time frame) and report characteristics (such as years	
16		considered, language, publication status) to be used as	
17		criteria for eligibility for the review	
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24	Information	#9 Describe all intended information sources (such as electronic	P9
25		databases, contact with study authors, trial registers or other	
26	sources	grey literature sources) with planned dates of coverage	
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32	Search strategy	#10 Present draft of search strategy to be used for at least one	P18
33		electronic database, including planned limits, such that it	
34		could be repeated	
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39	Study records -	#11a Describe the mechanism(s) that will be used to manage	P10-11
40		records and data throughout the review	
41	data management		
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45	Study records -	#11b State the process that will be used for selecting studies (such	P9-10
46		as two independent reviewers) through each phase of the	
47	selection process	review (that is, screening, eligibility and inclusion in meta-	
48		analysis)	
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54	Study records -	#11c Describe planned method of extracting data from reports	P10
55		(such as piloting forms, done independently, in duplicate), any	
56	data collection		
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1	process		processes for obtaining and confirming data from investigators	
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4	Data items	#12	List and define all variables for which data will be sought	P10
5			(such as PICO items, funding sources), any pre-planned data	
6			assumptions and simplifications	
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11	Outcomes and	#13	List and define all outcomes for which data will be sought,	P8
12				
13	prioritization		including prioritization of main and additional outcomes, with	
14			rationale	
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19	Risk of bias in	#14	Describe anticipated methods for assessing risk of bias of	P10-11
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21	individual studies		individual studies, including whether this will be done at the	
22			outcome or study level, or both; state how this information will	
23			be used in data synthesis	
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29	Data synthesis	#15a	Describe criteria under which study data will be quantitatively	P10-11
30			synthesised	
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34	Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe	P11
35			planned summary measures, methods of handling data and	
36			methods of combining data from studies, including any	
37			planned exploration of consistency (such as I ² , Kendall's τ)	
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44	Data synthesis	#15c	Describe any proposed additional analyses (such as	n/a
45			sensitivity or subgroup analyses, meta-regression)	
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49	Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type	n/a
50			of summary planned	
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54	Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as	P11
55			publication bias across studies, selective reporting within	
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studies)

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4 Confidence in [#17](#) Describe how the strength of the body of evidence will be n/a
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6 cumulative assessed (such as GRADE)
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8 evidence
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11 The PRISMA-P checklist is distributed under the terms of the Creative Commons Attribution License
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