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Global, regional and national prevalence of copper, selenium and zinc deficiencies in women of childbearing age: protocol for systematic review and meta-analysis.

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Complete List of Authors:	Costa, Priscila; Universidade Federal da Bahia Escola de Nutricao, Carvalho, Thais; Universidade Federal da Bahia Escola de Nutricao Pitangueira, Jacqueline ; Universidade Federal da Bahia Escola de Nutricao Santana, Mônica ; Universidade Federal da Bahia Escola de Nutricao Kinra, Sanjay; London School of Hygiene And Tropical Medicine, Potvin, Louise; University of Montreal
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Global, regional and national prevalence of copper, selenium and zinc deficiencies in women of childbearing age: protocol for systematic review and meta-analysis.

Authors

Dra. Priscila Ribas de Farias Costa; prfarias@ufba.br

PhD in Public Health (ISC/UFBA) with sandwich internship at LSHTM (University of London), MSc in Food, Nutrition and Health (ENUFBA), undergraduate in Nutrition (UFBA).

Thais Cerqueira de Carvalho; thais.cerqueira@ufba.com

Master's student in Food, Nutrition and Health (ENUFBA), undergraduate in Nutrition (UFBA).

Dra. Jacqueline Costa Dias Pitangueira; jack_cdias@hotmail.com

PhD in Medicine and Health (UFBA), MSc in Food, Nutrition and Health (ENUFBA), undergraduate in Nutrition (UFBA).

Dra. Mônica Leila Portela de Santana; monicalportela@gmail.com

PhD in Medicine and Health (UFBA), MSc in Science Applied to Pediatrics (UNIFESP), undergraduate in Nutrition (UFBA)

Dra. Sanjay Kinra; sanjay.kinra@lshtm.ac.uk

PhD in Epidemiology (University of Bristol), MFPHM in Public Health Medicine (Royal College of Physicians UK), MSc in Epidemiology (LSHTM, London), MD in Pediatrics (University of Delhi), MBBS in Medicine & Surgery (University of Delhi)

Dra. Louise Potvin; louise.potvin@umontreal.ca

PhD in Community Health (University of Montreal), M.A. Psychology (Concordia University, Montreal), member of the Steering Committee, principal investigator in the CIHR Centre Léa-Roback team.

Correspondence to:

Dra. Priscila Ribas de Farias Costa; prfarias@ufba.br;

PhD in Public Health (ISC/UFBA) with sandwich internship at LSHTM (University of London), MSc in Food, Nutrition and Health (ENUFBA), undergraduate in Nutrition (UFBA).

ABSTRACT

Introduction Micronutrient deficiencies are common in developing countries and are usually related to inadequate food intake, poor diet quality, and low bioavailability. Copper, selenium and zinc are essential minerals in several enzymatic reactions and their deficiencies are associated with worse prognosis in pregnancy, compromising maternal health as well as her offspring.

Methods and analysis The search will be performed by independent reviewers. The bases used will be PubMed/MEDLINE, Science direct, Lilacs, Adolec, Scopus, EMBASE, CINAHL, Web of Science, CENTRAL, IMSEAR, PAHOS, WPRIM, IMEMR, AIM for grey literature OpenGrey and OVID. National data will be searched in BDTD. Risk of bias assessment will be performed using the Joanna Briggs group prevalence study checklist. The Newcastle-Ottawa scale will be used to evaluate the methodological quality. Combinable studies will be performed meta-analysis. Heterogeneity will be tested using Cochran's Q test and quantified by the inconsistency test (I2). In the presence of high heterogeneity, meta-analysis will be performed using the random effects model with Stata metaprop. Summary prevalence will be generated for each outcome, presented in Forest plot figures.

Ethics and dissemination This systematic review will be solely based on published and retrievable literature, no ethics approval will be obtained. Our dissemination strategy will involve the presentation in scientific meetings, as well as the publication of article(s), posters and presentations in congresses.

PROSPERO Registration number CRD42020165352.

Keywords: Women, Fertility, Copper, Selenium, Zinc, systematic review, meta-analysis

Strengths and limitations of this study:

Micronutrient deficiency in women of childbearing age generates negative maternal health outcomes for their offspring. Considering that this is the first systematic review that will evaluate the prevalence of copper, selenium and zinc deficiencies in women of childbearing age worldwide, this is the main strength of the study. Also, this systematic review and meta-analysis has been carried out under rigorous methodology and following the recommendations of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)[1] and Cochrane Collaboration[2]

Considering the limitations, obtaining some articles in their entirety has been a challenge, as they are very old since we did not limit date for the publications. However, the authors have been contacted and some of them have sent the full articles.

BACKGROUND:

Micronutrient deficiencies are common in many developing countries and are usually related to inadequate food intake, poor diet quality, low bioavailability (due to the presence of inhibitors, preparation mode and interactions) and/or the presence of infections, and are of growing public health concern[3]. Although the focus of discussions on micronutrient deficiency is around three main problems-vitamin A deficiency (VAD), iodine deficiency disorders (IDD), and iron deficiency anemia (IDA)-with higher prevalences in low-income settings, zinc, selenium, and copper deficiencies have stood out as a cause for concern worldwide, regardless of socioeconomic status[4]. Copper, selenium and zinc are essential minerals in several enzymatic reactions and their deficiencies are associated with worse prognosis in pregnancy, compromising maternal health as well as her offspring[5–7].

Considering women of childbearing age, the consequences of deficiencies of these micronutrients affect not only these individuals, but also their offspring. These women are susceptible to maternal and fetal deficiencies, affecting future generations[8]. The developmental period in utero is critical for the health of the child, both at birth and long after. Micronutrient deficiencies in women of childbearing age can be exacerbated during pregnancy, increasing the risk of maternal and child complications. Maternal exposure to environmental hazards during pregnancy can therefore have a major impact on child health[9].

Thus, knowing the global, regional, and national prevalence of these nutritional deficiencies and their social determinants is of fundamental importance for planning policies and programs aimed at women's health in order to reduce the incidence of diseases associated with micronutrient deficiencies, as well as possible negative outcomes in pregnant women and infants.

METHODS AND ANALYSIS

Search strategy

This is the protocol of a systematic review with meta-analysis to identify the global, regional and national prevalence of zinc, selenium and copper deficiencies in women of childbearing age. The study will be developed based on the recommendations of PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol)[1] and the protocol has been registered in the International Prospective Register of Systematic Reviews (PROSPERO)[10].

The search will be performed by two independent reviewers (T.C.C and J.C.D.P). The controlled terms will be searched on the MeSH, Decs and ENTREE platforms. The search will be done in PubMed/MEDLINE, Science direct, LILACS, ADOLEC, Scopus, EMBASE, CINAHL, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), Index Medicus for the South-East Asia Region (IMSEAR), Pan American Health Organization (PAHOS), Index Medicus for the Western Pacific (WPRIM), Index Medicus of the Eastern Mediterranean (IMEMR) and African Index Medicus (AIM). In order to saturate the searches, manual searches will be conducted with analysis of reference lists of included articles and relevant reviews, contact with authors of included studies, study registries and grey literature in OpenGrey and OVID platforms. For national data approach, results of CAPES theses and dissertations and the Digital Library of Theses and Dissertations (BDTD) will be searched.

Inclusion criteria for study designs

Observational cohort or cross-sectional studies and intervention studies with data on micronutrient deficiency before the intervention and with women of childbearing age as the population group will be included.

Studies in which participants were supplemented with micronutrients (copper, selenium, and zinc) or studies in which participants were selected because they belonged to a group with chronic or high-risk diseases will be excluded. Due to inability to calculate prevalence, case-control articles will also be excluded. Review studies and case reports, in vitro and in vivo studies, book chapters, and any other studies that did not assess prevalence or provide data for possible calculations will also be excluded. There will be no limitations related to language or year of publication, and no search filters will be used.

Qualitative and quantitative studies will be searched, with no date limits, language of publication, or search filter. Search strategies will be developed by a Health Sciences Librarian with experience in systematic reviews. Every strategy will be developed with input from the project. An outline of the search strategy for the PUBMED platform is provided in Appendix 1.

Study selection

The entire search process will be exported to the Rayyan software (Rayyan QCRI/ web app), initiating the screening stage. Duplicate publications will be excluded to reduce the risk of bias. After this step, we will start reading the title and abstract to select the eligible publications

(step I). Studies meeting the criteria will be directed to full-text reading (step II); if necessary, reviewers will contact study authors to obtain additional information to help make the decision about study inclusion in the review. After reading the full text, only studies that meet the pre-established eligibility criteria will be selected. All these steps will be performed by two independent reviewers (T.C.C. and J.C.D.P.) and a third reviewer (P.R.F.C.) will be consulted in case of disagreement.

A flowchart will be prepared accounting for the total number of articles found in the search, selected for screening, eligible for reading in full, included and excluded from the review. After reading in full, all articles that do not meet the eligibility criteria will be excluded and the reasons for this decision will be reported in a spreadsheet to compose the flowchart of study selection. In the manual search, the reference lists of the included articles will be examined, as well as the reviews on the topic, and the team will decide together which studies will be selected for synthesis and data extraction.

Data extraction and data items

After reading and selecting the included articles, data synthesis and extraction will begin. The entire process will be documented in Microsoft Excel software. The information collected will be study identification, study characteristics, participant characteristics, diagnosis and classification of the condition, prevalence, incidence and factors associated with the condition, as presented in table 1.

Table 1 - Information collection

Identification of the study	Title, first author's last name, year of publication, journal, volume, number and pages.
Study characteristics	Participant recruitment period, country, region, study design, study site, study setting, sampling process, data collection time, sample size.
Participant Characteristics	Information on study inclusion and exclusion criteria, mean/median age,

	ethnicity, proportion of participants with any therapy.
Diagnosis and classification of the condition	Measurement or diagnostic criteria used to define the condition (micronutrient deficiency), micronutrient evaluated, unit of measurement, cut-off point adopted.
Prevalence and incidence	Number of participants, total person follow-up time, number of cases of the condition, reported etiologies, prevalence, incidence rate, and their respective confidence intervals and/or p-value.

In the absence of necessary information, the team will contact the authors of the study (maximum of three attempts by e-mail), and the entire process will be documented and logged. The identification of duplicate, overlapping, or complementary articles (multiple articles from the same study) will be performed by identifying the registration numbers of the clinical trials, the authors' names, the city and location of the study (institutions, schools, hospitals, etc.), specific details of the study methodology, date and duration of the study (when applicable). If questions remain, the authors of the articles will be contacted.

Every extraction step will be performed by two previously trained reviewers. Legends will be elaborated with the objective of simplifying the data extraction spreadsheet.

Outcome assessment

The main outcome of this review is the identification of the global, regional (by continent) and national prevalence of zinc, selenium and copper deficiencies in women of childbearing age. These results can serve as a reference for the production of other works in the area, besides making public relevant data on women's health worldwide, supporting citations of this content by other authors, thus increasing the visibility of scientific production and contributing to the knowledge about the deficiency of these micronutrients in the target audience.

Risk of bias assessment strategy

The evaluation of the risk of bias will be performed using the critical appraisal checklist for prevalence studies[11]. This checklist contains 10 items of questions regarding the sample, data collection, and statistical procedures used in the study. The response options are "yes", "no", "unclear" or "not applicable". The Newcastle-Ottawa scale will be used to evaluate the methodological quality.

All studies, regardless of their quality score, will be included in this review and the sensitivity analysis will assess the relevance of methodological quality in the final result. Both steps will be performed independently by two experienced and trained reviewers, and in case of disagreement a third reviewer will break the tie.

Analysis, data synthesis, publication bias and reporting

From these extracted data, a qualitative synthesis will be carried out structured around the prevalence of the deficiencies/inabilities identified in the studies, measurement units and cutoff points adopted, evaluating these results by country and socioeconomic situation (low, lower-middle, upper-middle, and high income countries).

For combinatorial studies[2], quantitative synthesis of data will be performed using meta-analysis. The extent of heterogeneity of the meta-analysis will be tested using Cochran's Q test and quantified by the inconsistency test (I^2 statistic). This statistic determines the magnitude of heterogeneity by the proportion of the total variation between studies due to heterogeneity[2]. A p-value is often cited as an indication of the extent of variability between studies. Therefore, the chi-square test will be employed to assess the significance of heterogeneity. A significance level of p-value <0.10 will be used to detect true heterogeneity among study results[2].

The magnitude of heterogeneity will be identified by calculating I^2, which ranges from 0 to 100%. Thus, I^2 close to zero suggests that all the dispersion can be attributed to the random error of the study, i.e., there is no heterogeneity. If an I^2 value close to 25% is calculated, it indicates low heterogeneity among studies; higher than 50% indicates moderate heterogeneity; and, above 75%, high heterogeneity[2].

In the presence of high heterogeneity, meta-analysis will be performed using the random effects model conducted with Stata's metaprop command. It allows the computation of 95% confidence intervals using the score statistic and the exact binomial method, as well as incorporating FreemanTukey's double-sine-arc transformation of proportions. This method also

allows you to model intra-study variability using the binomial distribution. That is, it makes the data distribution normal and stabilizes variances[12]. The inverse function of the double sine-arc transformation has also been derived in the literature to recover the original proportion scale after data aggregation[12] while maintaining the interpretability of the final result. Thus, we will generate the summary prevalence for each outcome, as well as its respective 95% confidence interval, presented in Forest plot figures.

Potential variables that may influence the high heterogeneity among studies will be investigated by means of subgroup analysis (for dichotomous variables: age group, ethnicity, socioeconomic status, dosage form [blood or serum], cutoff point adopted, and anthropometric status) and meta-regression (for continuous variables: mean age, sample size, and mean BMI).

If ten or more studies are included in the meta-analysis, Egger's test and the funnel plot will be adopted to assess publication bias. In the funnel plot, the graphic funnel shape makes a qualitative assessment of the possibility of bias, in which asymmetries indicate the presence of publication bias. Egger's test will be applied when the variables are dichotomous or when the distribution of effects is normal (continuous variables); otherwise (asymmetric distribution), Begg's test will be applied. A strong probability that the distribution is not by chance, i.e., presence of publication bias, is suggested when p value <0.05[2].

Ethics, dissemination data protection

Ethical approval was not obtained since the data to be collected and analyzed cannot be linked to specific individuals.

Patient and public involvement

Since this will be a systematic review, there will be no direct patient or public involvement.

Ethics and dissemination

This systematic review will allow the identification of the prevalence of copper, selenium and zinc deficiencies in women of childbearing age at the global, regional and national (Brazil) levels and will serve as a reference for the production of other works in the area, besides making public relevant data on women's health in Brazil and in the world, supporting citations of this content by other authors, thus increasing the visibility of the national scientific production and the Brazilian contribution to the world scientific knowledge.

Our dissemination strategy will involve the presentation in scientific meetings, as well as the publication of article(s) in international journals, peer-reviewed and open access, preparation of posters and oral presentations in Congresses and scientific events at national and international level, in the areas of nutrition and public health.

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Contributions: P.R.C.F. supervised the study and contributed to study conception, design, and manuscript drafting. T.C.C contributed to study conception, design, and manuscript drafting. J.C.D.P. contributed to study conception, design, and manuscript drafting. M.L.P.S contributed to study conception, design, and manuscript drafting. S.K. contributed to study conception, design, and manuscript drafting. L.P contributed to study conception, design, and manuscript drafting. All authors critically reviewed and approved the final manuscript for submission.

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Competing interests: This research has no conflict of interest.

Patient consent for publication: Not required.

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REFERENCES

1. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Revista Espanola de Nutricion Humana y Dietetica*. 2016;20(2):148-160. doi:10.1186/2046-4053-4-1
2. Higgins J, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions. version 6.3. Published 2022. Accessed July 3, 2021. www.training.cochrane.org/handbook
3. Ramakrishnan U, Ph D. Prevalence of Micronutrient Malnutrition Worldwide. *Nutrition Reviews*. 2002;(May):S46–S52. doi:https://doi-org.eres.qnl.qa/10.1301/00296640260130731
4. Magee, Pamela J; McCann MT. Conference on ' Targeted approaches to tackling current nutritional issues ' Micronutrient de fi ciencies : current issues. *Proceeding of the Nutrition Society*. Published online 2018:147-149. doi:10.1017/S0029665118002677
5. Mariath AB. *Efeitos Da Suplementação de Selênio Durante a Gestação : Uma Revisão Sistemática*. Faculdade de Saúde Pública; 2010. doi:10.11606/D.6.2010.tde-12112010-144009
6. Nascimento DA. *Valores de Referência Para Cobre e Zinco No Plas e No Eritrócito Em Adultos Universitários Na Cidade de Natal-RN*. UNIVERSIDADE FEDERAL DO RIO GRANDE DO NORTE; 2006. https://repositorio.ufrn.br/jspui/handle/123456789/13441
7. Cozzolino SMF. MINERAL BIO V AIL ABILITY. *Nutrição Campinas*. 1997;10(011):87-98.
8. Panth P, Guerin G, DiMarco NM. A Review of Iodine Status of Women of Reproductive Age in the USA. *Biological Trace Element Research*. 2019;188(1):208-220. doi:10.1007/s12011-018-1606-5
9. Simpson JOEL, Bailey LB, Pietrzik K, Shane B, Holzgreve W. Micronutrients and women of reproductive potential : required dietary intake and consequences of dietary deficiency or excess . Part I – Folate , Vitamin B12 , Vitamin B6. 2010;23(December):1323-1343. doi:10.3109/14767051003678234
10. Ribas De Farias Costa P, Santana L, Potvin L, et al. *PROSPERO*. Accessed June 30, 2022. https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=165352
11. Aromataris E MZ. JBI Manual for Evidence Synthesis. doi:https://doi.org/10.46658/JBIMES-20-01
12. Jeong J hyeon. Domain of Inverse Double Arcsine Transformation. 2018;1(1):2-5.

Appendix 1

Example of a draft search in the PUBMED database.

Search**: #1- (Childbearing age) OR (Reproductive Age) OR (Age, Reproductive)**

Search**: #2 - (Copper) OR (Copper status)**

Search**: #3 - (Selenium) OR (Selenium status)**

Search**: #4 - (Zinc) OR (Zinc status)**

#1 AND #2

((("childbearers"[All Fields] OR "childbearing"[All Fields]) AND ("age"[Journal] OR "age omaha"[Journal] OR "age dordr"[Journal] OR "adv genet eng"[Journal] OR "age"[All Fields])) OR (("reproduction"[MeSH Terms] OR "reproduction"[All Fields] OR "reproductions"[All Fields] OR "reproductive"[All Fields] OR "reproductively"[All Fields] OR "reproductives"[All Fields] OR "reproductivity"[All Fields]) AND ("age"[Journal] OR "age omaha"[Journal] OR "age dordr"[Journal] OR "adv genet eng"[Journal] OR "age"[All Fields])) OR (("age"[Journal] OR "age omaha"[Journal] OR "age dordr"[Journal] OR "adv genet eng"[Journal] OR "age"[All Fields]) AND ("reproduction"[MeSH Terms] OR "reproduction"[All Fields] OR "reproductions"[All Fields] OR "reproductive"[All Fields] OR "reproductively"[All Fields] OR "reproductives"[All Fields] OR "reproductivity"[All Fields]))) AND ("copper"[MeSH Terms] OR "copper"[All Fields] OR "coppers"[All Fields] OR "copper s"[All Fields] OR (("copper"[MeSH Terms] OR "copper"[All Fields] OR "coppers"[All Fields] OR "copper s"[All Fields]) AND "status"[All Fields]))

#1 AND #3

((("childbearers"[All Fields] OR "childbearing"[All Fields]) AND ("age"[Journal] OR "age omaha"[Journal] OR "age dordr"[Journal] OR "adv genet eng"[Journal] OR "age"[All Fields])) OR (("reproduction"[MeSH Terms] OR "reproduction"[All Fields] OR "reproductions"[All Fields] OR "reproductive"[All Fields] OR "reproductively"[All Fields] OR "reproductives"[All Fields] OR "reproductivity"[All Fields]) AND ("age"[Journal] OR "age omaha"[Journal] OR "age dordr"[Journal] OR "adv genet eng"[Journal] OR "age"[All Fields])) OR (("age"[Journal] OR "age omaha"[Journal]

OR "age dordr"[Journal] OR "adv genet eng"[Journal] OR "age"[All Fields]) AND ("reproduction"[MeSH Terms] OR "reproduction"[All Fields] OR "reproductions"[All Fields] OR "reproductive"[All Fields] OR "reproductively"[All Fields] OR "reproductives"[All Fields] OR "reproductivity"[All Fields])) AND ("selenium"[MeSH Terms] OR "selenium"[All Fields] OR "selenium s"[All Fields] OR "seleniums"[All Fields] OR (("selenium"[MeSH Terms] OR "selenium"[All Fields] OR "selenium s"[All Fields] OR "seleniums"[All Fields]) AND "status"[All Fields]))

#1 AND #4

((("childbearers"[All Fields] OR "childbearing"[All Fields]) AND ("age"[Journal] OR "age omaha"[Journal] OR "age dordr"[Journal] OR "adv genet eng"[Journal] OR "age"[All Fields])) OR (("reproduction"[MeSH Terms] OR "reproduction"[All Fields] OR "reproductions"[All Fields] OR "reproductive"[All Fields] OR "reproductively"[All Fields] OR "reproductives"[All Fields] OR "reproductivity"[All Fields]) AND ("age"[Journal] OR "age omaha"[Journal] OR "age dordr"[Journal] OR "adv genet eng"[Journal] OR "age"[All Fields])) OR (("age"[Journal] OR "age omaha"[Journal] OR "age dordr"[Journal] OR "adv genet eng"[Journal] OR "age"[All Fields]) AND ("reproduction"[MeSH Terms] OR "reproduction"[All Fields] OR "reproductions"[All Fields] OR "reproductive"[All Fields] OR "reproductively"[All Fields] OR "reproductives"[All Fields] OR "reproductivity"[All Fields]))) AND ("zinc"[MeSH Terms] OR "zinc"[All Fields] OR (("zinc"[MeSH Terms] OR "zinc"[All Fields]) AND "status"[All Fields]))

Reporting checklist for protocol of a systematic review and meta analysis.

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-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	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	1

Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	10
Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support			
Sources	#5a	Indicate sources of financial or other support for the review	10
Sponsor	#5b	Provide name for the review funder and / or sponsor	10
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	10
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is	4

		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)	4-5
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	5
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	5
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	5
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	5-6
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)	5-6
Study records - data collection	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any	6-7

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	6-7
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7-8
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	8
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)	8
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8-9
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8-9
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within	9

		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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Authors

Dra. Priscila Ribas de Farias Costa; prfarias@ufba.br

PhD in Public Health (ISC/UFBA) with sandwich internship at LSHTM (University of London), MSc in Food, Nutrition and Health (ENUFBA), undergraduate in Nutrition (UFBA).

Thais Cerqueira de Carvalho; thais.cerqueira@ufba.com

Master's student in Food, Nutrition and Health (ENUFBA), undergraduate in Nutrition (UFBA).

Dra. Jacqueline Costa Dias Pitangueira; jack_cdias@hotmail.com

PhD in Medicine and Health (UFBA), MSc in Food, Nutrition and Health (ENUFBA), undergraduate in Nutrition (UFBA).

Dra. Mônica Leila Portela de Santana; monicalportela@gmail.com

PhD in Medicine and Health (UFBA), MSc in Science Applied to Pediatrics (UNIFESP), undergraduate in Nutrition (UFBA)

Dra. Sanjay Kinra; sanjay.kinra@lshtm.ac.uk

PhD in Epidemiology (University of Bristol), MFPHM in Public Health Medicine (Royal College of Physicians UK), MSc in Epidemiology (LSHTM, London), MD in Pediatrics (University of Delhi), MBBS in Medicine & Surgery (University of Delhi)

Dra. Louise Potvin; louise.potvin@umontreal.ca

PhD in Community Health (University of Montreal), M.A. Psychology (Concordia University, Montreal), member of the Steering Committee, principal investigator in the CIHR Centre Léa-Roback team.

Correspondence to:

Dra. Priscila Ribas de Farias Costa; prfarias@ufba.br;

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ABSTRACT

Introduction Micronutrient deficiencies are common in developing countries and are usually related to inadequate food intake, poor diet quality, and low bioavailability. Copper, selenium and zinc are essential minerals in several enzymatic reactions and their deficiencies are associated with worse prognosis in pregnancy, compromising maternal health as well as her offspring.

Methods and analysis The search will be performed by independent reviewers. The bases used will be PubMed/MEDLINE, Science direct, Lilacs, Adolec, Scopus, EMBASE, CINAHL, Web of Science, CENTRAL, IMSEAR, PAHOS, WPRIM, IMEMR, AIM for grey literature OpenGrey and OVID. National data will be searched in BDTD. All search was performed on 10/2021 and updated on 10/2022. Risk of bias assessment will be performed using the Joanna Briggs group prevalence study checklist. Combinable studies will be performed meta-analysis. Heterogeneity will be tested using Cochran's Q test and quantified by the inconsistency test (I^2). In the presence of high heterogeneity, meta-analysis will be performed using the random effects model with Stata metaprop. Summary prevalence will be generated for each outcome, presented in Forest plot figures.

Ethics and dissemination This systematic review will be solely based on published and retrievable literature, no ethics approval will be obtained. Our dissemination strategy will involve the presentation in scientific meetings, as well as the publication of article(s), posters and presentations in congresses.

PROSPERO Registration number CRD42020165352.

Keywords: Women, Fertility, Copper, Selenium, Zinc, systematic review, meta-analysis

Strengths and limitations of this study:

- First systematic review that will assess the prevalence of copper, selenium and zinc deficiencies in women of childbearing age worldwide.
- A thorough and highly sensitive search strategy in leading databases, with no geographic or language restrictions, will be conducted by a multidisciplinary team with experience in systematic review.
- Different cut-off points.
- Heterogeneity among studies.

BACKGROUND:

Micronutrient deficiencies are common in many developing countries and are usually related to inadequate food intake, poor diet quality, low bioavailability (due to the presence of inhibitors, preparation mode and interactions) and/or the presence of infections, and are of growing public health concern[1,2]. Although the focus of discussions on micronutrient deficiency is around three main problems-vitamin A deficiency (VAD), iodine deficiency disorders (IDD), and iron deficiency anemia (IDA)-with higher prevalences in low-income settings, zinc, selenium, and copper deficiencies have stood out as a cause for concern worldwide, regardless of socioeconomic status[2,3]. Copper, selenium and zinc are essential minerals in several enzymatic reactions and their deficiencies may be associated with worse prognosis in pregnancy. Deficiencies may increase the risk of premature labor. But there are still contradictions[4–6].

Considering women of childbearing age, the consequences of deficiencies of these micronutrients can affect not only these individuals, but also their offspring. These women are susceptible to maternal and fetal deficiencies, affecting future generations[7]. The developmental period in utero is critical for the health of the child, both at birth and long after. Micronutrient deficiencies in women of childbearing age can be exacerbated during pregnancy, increasing the risk of maternal and child complications[2]. Maternal exposure to environmental hazards during pregnancy can therefore have a major impact on child health[8].

Thus, knowing the global, regional, and national prevalence of these nutritional deficiencies and their social determinants is of fundamental importance for planning policies and programs aimed at women's health in order to reduce the incidence of diseases associated with micronutrient deficiencies, as well as possible negative outcomes in pregnant women and infants.

Question formulation: What is the prevalence of copper, selenium and zinc deficiencies in women of childbearing age?

METHODS AND ANALYSIS

Search strategy

This is the protocol of a systematic review with meta-analysis to identify the global, regional and national prevalence of zinc, selenium and copper deficiencies in women of childbearing age. The study will be developed based on the recommendations of PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol)[9] and the protocol

has been registered in the International Prospective Register of Systematic Reviews (PROSPERO)[10].

The search will be performed by two independent reviewers (T.C.C and J.C.D.P) and a third reviewer (P.R.F.C.) will be consulted in case of disagreement. The controlled terms will be searched on the MeSH, Decs and ENTREE platforms. The search will be done in PubMed/MEDLINE, Science direct, LILACS, ADOLEC, Scopus, EMBASE, CINAHL, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), Index Medicus for the South-East Asia Region (IMSEAR), Pan American Health Organization (PAHOS), Index Medicus for the Western Pacific (WPRIM), Index Medicus of the Eastern Mediterranean (IMEMR) and African Index Medicus (AIM). In order to saturate the searches, manual searches will be conducted with analysis of reference lists of included articles and relevant reviews, contact with authors of included studies, study registries and grey literature in OpenGrey and OVID platforms. For national data approach, results of CAPES theses and dissertations and the Digital Library of Theses and Dissertations (BDTD) will be searched. All search was performed on 10/2021 and updated on 10/2022.

Inclusion criteria for study designs

Observational cohort or cross-sectional studies and intervention studies with data on micronutrient deficiency before the intervention and with women of childbearing age as the population group will be included. Although most studies consider fertile age 15 to 49 years[11–13]. In this study, this group will be 10 and 49 years old, by request of the Brazilian Ministry of Health.

Studies in which participants were supplemented with micronutrients (copper, selenium, and zinc) or studies in which participants were selected because they belonged to a group with chronic or high-risk diseases will be excluded. Due to inability to calculate prevalence, case-control articles will also be excluded. Review studies and case reports, in vitro and in vivo studies, book chapters, and any other studies that did not assess prevalence or provide data for possible calculations will also be excluded. There will be no limitations related to language or year of publication, and no search filters will be used.

Qualitative and quantitative studies will be searched, with no date limits, language of publication, or search filter. Search strategies will be developed by a Health Sciences Librarian with experience in systematic reviews. Every strategy will be developed with input from the project. An outline of the search strategy for the PUBMED platform is provided in Appendix 1.

Study selection

The entire search process will be exported to the Rayyan software (Rayyan QCRI/ web app), initiating the screening stage. Duplicate publications will be excluded to reduce the risk of bias. After this step, we will start reading the title and abstract to select the eligible publications (step I). Studies meeting the criteria will be directed to full-text reading (step II); if necessary, reviewers will contact study authors to obtain additional information to help make the decision about study inclusion in the review. After reading the full text, only studies that meet the pre-established eligibility criteria will be selected. All these steps will be performed by two independent reviewers (T.C.C. and J.C.D.P.) and a third reviewer (P.R.F.C.) will be consulted in case of disagreement.

A flowchart will be prepared accounting for the total number of articles found in the search, selected for screening, eligible for reading in full, included and excluded from the review. After reading in full, all articles that do not meet the eligibility criteria will be excluded and the reasons for this decision will be reported in a spreadsheet to compose the flowchart of study selection. In the manual search, the reference lists of the included articles will be examined, as well as the reviews on the topic, and the team will decide together which studies will be selected for synthesis and data extraction.

Data extraction and data items

After reading and selecting the included articles, data synthesis and extraction will begin. The entire process will be documented in Microsoft Excel software. The information collected will be study identification, study characteristics, participant characteristics, diagnosis and classification of the condition, prevalence, incidence and factors associated with the condition, as presented in table 1.

Table 1 - Information collection

Identification of the study	Title, first author's last name, year of publication, journal, volume, number and pages.
Study characteristics	Participant recruitment period, country, region, study design, study site, study

	setting, sampling process, data collection time, sample size.
Participant Characteristics	Information on study inclusion and exclusion criteria, mean/median age, ethnicity, proportion of participants with any therapy.
Diagnosis and classification of the condition	Measurement or diagnostic criteria used to define the condition (micronutrient deficiency), micronutrient evaluated, unit of measurement, cut-off point adopted.
Prevalence and incidence	Number of participants, total person follow-up time, number of cases of the condition, reported etiologies, prevalence, incidence rate, and their respective confidence intervals and/or p-value.

In the absence of necessary information, the team will contact the authors of the study (maximum of three attempts by e-mail), and the entire process will be documented and logged. The identification of duplicate, overlapping, or complementary articles (multiple articles from the same study) will be performed by identifying the registration numbers of the clinical trials, the authors' names, the city and location of the study (institutions, schools, hospitals, etc.), specific details of the study methodology, date and duration of the study (when applicable). If questions remain, the authors of the articles will be contacted.

Every extraction step will be performed by two previously trained reviewers. Legends will be elaborated with the objective of simplifying the data extraction spreadsheet.

Outcome assessment

The main outcome of this review is the identification of the global, regional (by continent) and national prevalence of zinc, selenium and copper deficiencies in women of childbearing age. These results can serve as a reference for the production of other works in the area, besides making public relevant data on women's health worldwide, supporting citations of this content by other

authors, thus increasing the visibility of scientific production and contributing to the knowledge about the deficiency of these micronutrients in the target audience.

Risk of bias assessment strategy

The evaluation of the risk of bias will be performed using the critical appraisal checklist for prevalence studies[14]. This checklist contains 9 items of questions regarding the sample, data collection, and statistical procedures used in the study. The response options are "yes", "no", "unclear" or "not applicable". The Newcastle-Ottawa scale will be used to evaluate the methodological quality[15].

All studies, regardless of their quality score, will be included in this review and the sensitivity analysis will assess the relevance of methodological quality in the final result. Both steps will be performed independently by two experienced and trained reviewers, and in case of disagreement a third reviewer will break the tie.

Analysis, data synthesis, publication bias and reporting

From these extracted data, a qualitative synthesis will be carried out structured around the prevalence of the deficiencies/inabilities identified in the studies, measurement units and cutoff points adopted, evaluating these results by country and socioeconomic situation (low, lower-middle, upper-middle, and high income countries).

For combinatorial studies[16], quantitative synthesis of data will be performed using meta-analysis. The extent of heterogeneity of the meta-analysis will be tested using Cochran's Q test and quantified by the inconsistency test (I^2 statistic). This statistic determines the magnitude of heterogeneity by the proportion of the total variation between studies due to heterogeneity[16]. A p-value is often cited as an indication of the extent of variability between studies. Therefore, the chi-square test will be employed to assess the significance of heterogeneity. A significance level of p-value <0.10 will be used to detect true heterogeneity among study results[16].

The magnitude of heterogeneity will be identified by calculating I^2, which ranges from 0 to 100%. Thus, I^2 close to zero suggests that all the dispersion can be attributed to the random error of the study, i.e., there is no heterogeneity. If an I^2 value close to 25% is calculated, it indicates low heterogeneity among studies; higher than 50% indicates moderate heterogeneity; and, above 75%, high heterogeneity[16].

In the presence of high heterogeneity, meta-analysis will be performed using the random effects model conducted with Stata's metaprop command. It allows the computation of 95% confidence intervals using the score statistic and the exact binomial method, as well as incorporating FreemanTukey's double-sine-arc transformation of proportions. This method also allows you to model intra-study variability using the binomial distribution. That is, it makes the data distribution normal and stabilizes variances[17]. The inverse function of the double sine-arc transformation has also been derived in the literature to recover the original proportion scale after data aggregation[17] while maintaining the interpretability of the final result. Thus, we will generate the summary prevalence for each outcome, as well as its respective 95% confidence interval, presented in Forest plot figures.

Potential variables that may influence the high heterogeneity among studies will be investigated by means of subgroup analysis (for dichotomous variables: age group, ethnicity, socioeconomic status, dosage form [blood or serum], cutoff point adopted, and anthropometric status) and meta-regression (for continuous variables: mean age, sample size, and mean BMI).

If ten or more studies are included in the meta-analysis, Egger's test and the funnel plot will be adopted to assess publication bias. In the funnel plot, the graphic funnel shape makes a qualitative assessment of the possibility of bias, in which asymmetries indicate the presence of publication bias. Egger's test will be applied when the variables are dichotomous or when the distribution of effects is normal (continuous variables); otherwise (asymmetric distribution), Begg's test will be applied. A strong probability that the distribution is not by chance, i.e., presence of publication bias, is suggested when p value <0.05[16].

Ethics, dissemination data protection

Ethical approval was not obtained since the data to be collected and analyzed cannot be linked to specific individuals.

Patient and public involvement

Since this will be a systematic review, there will be no direct patient or public involvement.

Ethics and dissemination

This systematic review will allow the identification of the prevalence of copper, selenium and zinc deficiencies in women of childbearing age at the global, regional and national (Brazil)

levels and will serve as a reference for the production of other works in the area, besides making public relevant data on women's health in Brazil and in the world, supporting citations of this content by other authors, thus increasing the visibility of the national scientific production and the Brazilian contribution to the world scientific knowledge.

Our dissemination strategy will involve the presentation in scientific meetings, as well as the publication of article(s) in international journals, peer-reviewed and open access, preparation of posters and oral presentations in Congresses and scientific events at national and international level, in the areas of nutrition and public health.

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Contributions: P.R.C.F. supervised the study and contributed to study conception, design, and manuscript drafting. T.C.C contributed to study conception, design, and manuscript drafting. J.C.D.P. contributed to study conception, design, and manuscript drafting. M.L.P.S contributed to study conception, design, and manuscript drafting. S.K. contributed to study conception, design, and manuscript drafting. L.P contributed to study conception, design, and manuscript drafting. All authors critically reviewed and approved the final manuscript for submission.

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Competing interests: This research has no conflict of interest.

Patient consent for publication: Not required.

Word Count: 2.240

REFERENCES

1. Ramakrishnan U, Ph D. Prevalence of Micronutrient Malnutrition Worldwide. *Nutr Rev*. 2002;(May):S46–S52. doi:https://doi-org.eres.qnl.qa/10.1301/00296640260130731

2. Pobee RA, Aguree S, Komeley Colecraft E, Gernand AD, Murray-Kolb LE. Food Insecurity and Micronutrient Status among Ghanaian Women Planning to Become Pregnant. Published online 2020. doi:10.3390/nu12020470

3. Magee, Pamela J; McCann MT. Conference on ' Targeted approaches to tackling current nutritional issues ' Micronutrient de fi ciencies : current issues. *Proceeding of the Nutrition Society*. Published online 2018:147-149. doi:10.1017/S0029665118002677

4. Monangi N, Xu H, Khanam R, et al. Association of maternal prenatal selenium concentration and preterm birth: a multicountry meta-analysis. *BMJ Glob Health*. 2021;6(9):e005856. doi:10.1136/BMJGH-2021-005856

5. Barman M, Brantsæter AL, Nilsson S, et al. Maternal dietary selenium intake is associated with increased gestational length and decreased risk of preterm delivery. *British Journal of Nutrition*. 2020;123(2):209-219. doi:10.1017/S0007114519002113

6. Zhang X, Feng YJ, Li J, et al. Maternal selenium deficiency during gestation is positively associated with the risks for LBW and SGA newborns in a Chinese population. *Eur J Clin Nutr*. 2021;75(5):768-774. doi:10.1038/s41430-020-00809-x

7. Panth P, Guerin G, DiMarco NM. A Review of Iodine Status of Women of Reproductive Age in the USA. *Biol Trace Elem Res*. 2019;188(1):208-220. doi:10.1007/s12011-018-1606-5

8. Simpson JOEL, Bailey LB, Pietrzik K, Shane B, Holzgreve W. Micronutrients and women of reproductive potential : required dietary intake and consequences of dietary deficiency or excess . Part I – Folate , Vitamin B12 , Vitamin B6. 2010;23(December):1323-1343. doi:10.3109/14767051003678234

9. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Revista Espanola de Nutricion Humana y Dietetica*. 2016;20(2):148-160. doi:10.1186/2046-4053-4-1

10. Ribas De Farias Costa P, Santana L, Potvin L, et al. *PROSPERO*. Accessed June 30, 2022. https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=165352

11. Stevens GA, Beal T, Mbuya MNN, et al. Micronutrient deficiencies among preschool-aged children and women of reproductive age worldwide: a pooled analysis of individual-level data from population-representative surveys. *Lancet Glob Health*. 2022;10(11):e1590-e1599. doi:10.1016/S2214-109X(22)00367-9

12. Gupta S, Brazier AKM, Lowe NM. Zinc deficiency in low- and middle-income countries: prevalence and approaches for mitigation. *Journal of Human Nutrition and Dietetics*. 2020;33(5):624-643. doi:10.1111/jhn.12791

13. Belay A, Gashu D, Joy EJM, et al. Mineral micronutrient status and spatial distribution among the Ethiopian population. doi:10.1017/S0007114522000319

14. Aromataris E MZ. JBI Manual for Evidence Synthesis. doi:https://doi.org/10.46658/JBIMES-20-01

15. Munn Z, MClinSc SM, Lisy K, Riitano D, Tufanaru C. Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data. *Int J Evid Based Healthc*. 2015;13(3):147-153. doi:10.1097/XEB.0000000000000054

16. Higgins J, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions. version 6.3. Published 2022. Accessed July 3, 2021. www.training.cochrane.org/handbook

17. Jeong J hyeon. Domain of Inverse Double Arcsine Transformation. 2018;1(1):2-5.

Appendix 1

Example of a draft search in the PUBMED database.

Search**: #1- (Childbearing age) OR (Reproductive Age) OR (Age, Reproductive)**

Search**: #2 - (Copper) OR (Copper status)**

Search**: #3 - (Selenium) OR (Selenium status)**

Search**: #4 - (Zinc) OR (Zinc status)**

#1 AND #2

((("childbearers"[All Fields] OR "childbearing"[All Fields]) AND ("age"[Journal] OR "age omaha"[Journal] OR "age dordr"[Journal] OR "adv genet eng"[Journal] OR "age"[All Fields])) OR (("reproduction"[MeSH Terms] OR "reproduction"[All Fields] OR "reproductions"[All Fields] OR "reproductive"[All Fields] OR "reproductively"[All Fields] OR "reproductives"[All Fields] OR "reproductivity"[All Fields]) AND ("age"[Journal] OR "age omaha"[Journal] OR "age dordr"[Journal] OR "adv genet eng"[Journal] OR "age"[All Fields])) OR (("age"[Journal] OR "age omaha"[Journal] OR "age dordr"[Journal] OR "adv genet eng"[Journal] OR "age"[All Fields]) AND ("reproduction"[MeSH Terms] OR "reproduction"[All Fields] OR "reproductions"[All Fields] OR "reproductive"[All Fields] OR "reproductively"[All Fields] OR "reproductives"[All Fields] OR "reproductivity"[All Fields]))) AND ("copper"[MeSH Terms] OR "copper"[All Fields] OR "coppers"[All Fields] OR "copper s"[All Fields] OR (("copper"[MeSH Terms] OR "copper"[All Fields] OR "coppers"[All Fields] OR "copper s"[All Fields]) AND "status"[All Fields]))

#1 AND #3

((("childbearers"[All Fields] OR "childbearing"[All Fields]) AND ("age"[Journal] OR "age omaha"[Journal] OR "age dordr"[Journal] OR "adv genet eng"[Journal] OR "age"[All Fields])) OR (("reproduction"[MeSH Terms] OR "reproduction"[All Fields] OR "reproductions"[All Fields] OR "reproductive"[All Fields] OR "reproductively"[All Fields] OR "reproductives"[All Fields] OR "reproductivity"[All Fields]) AND ("age"[Journal] OR "age omaha"[Journal] OR "age dordr"[Journal] OR "adv genet eng"[Journal] OR "age"[All Fields])) OR (("age"[Journal] OR "age omaha"[Journal]

OR "age dordr"[Journal] OR "adv genet eng"[Journal] OR "age"[All Fields]) AND ("reproduction"[MeSH Terms] OR "reproduction"[All Fields] OR "reproductions"[All Fields] OR "reproductive"[All Fields] OR "reproductively"[All Fields] OR "reproductives"[All Fields] OR "reproductivity"[All Fields])) AND ("selenium"[MeSH Terms] OR "selenium"[All Fields] OR "selenium s"[All Fields] OR "seleniums"[All Fields] OR (("selenium"[MeSH Terms] OR "selenium"[All Fields] OR "selenium s"[All Fields] OR "seleniums"[All Fields]) AND "status"[All Fields]))

#1 AND #4

((("childbearers"[All Fields] OR "childbearing"[All Fields]) AND ("age"[Journal] OR "age omaha"[Journal] OR "age dordr"[Journal] OR "adv genet eng"[Journal] OR "age"[All Fields])) OR (("reproduction"[MeSH Terms] OR "reproduction"[All Fields] OR "reproductions"[All Fields] OR "reproductive"[All Fields] OR "reproductively"[All Fields] OR "reproductives"[All Fields] OR "reproductivity"[All Fields]) AND ("age"[Journal] OR "age omaha"[Journal] OR "age dordr"[Journal] OR "adv genet eng"[Journal] OR "age"[All Fields])) OR (("age"[Journal] OR "age omaha"[Journal] OR "age dordr"[Journal] OR "adv genet eng"[Journal] OR "age"[All Fields]) AND ("reproduction"[MeSH Terms] OR "reproduction"[All Fields] OR "reproductions"[All Fields] OR "reproductive"[All Fields] OR "reproductively"[All Fields] OR "reproductives"[All Fields] OR "reproductivity"[All Fields]))) AND ("zinc"[MeSH Terms] OR "zinc"[All Fields] OR (("zinc"[MeSH Terms] OR "zinc"[All Fields]) AND "status"[All Fields]))

Reporting checklist for protocol of a systematic review and meta analysis.

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-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	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	1

Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	9
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	9
Sponsor	#5b	Provide name for the review funder and / or sponsor	9
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	9
Introduction			

Rationale	#6	Describe the rationale for the review in the context of what is already known	3
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	3
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	3-4
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	4
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	4
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	5
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)	4-5

Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	5-6
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	5-6
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6-7
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	7
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	7
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)	7
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8

Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	n/a

BMJ Open

Global, regional and national prevalence of copper, selenium and zinc deficiencies in women of childbearing age: protocol for systematic review and meta-analysis.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-066324.R2
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Primary Subject Heading:	Nutrition and metabolism
Secondary Subject Heading:	Epidemiology, Nutrition and metabolism, Public health
Keywords:	NUTRITION & DIETETICS, EPIDEMIOLOGY, PUBLIC HEALTH

Global, regional and national prevalence of copper, selenium and zinc deficiencies in women of childbearing age: protocol for systematic review and meta-analysis.

Authors

Dra. Priscila Ribas de Farias Costa; prfarias@ufba.br

PhD in Public Health (ISC/UFBA) with sandwich internship at LSHTM (University of London), MSc in Food, Nutrition and Health (ENUFBA), undergraduate in Nutrition (UFBA).

Thais Cerqueira de Carvalho; thais.cerqueira@ufba.com

Master's student in Food, Nutrition and Health (ENUFBA), undergraduate in Nutrition (UFBA).

Dra. Jacqueline Costa Dias Pitangueira; jack_cdias@hotmail.com

PhD in Medicine and Health (UFBA), MSc in Food, Nutrition and Health (ENUFBA), undergraduate in Nutrition (UFBA).

Dra. Mônica Leila Portela de Santana; monicalportela@gmail.com

PhD in Medicine and Health (UFBA), MSc in Science Applied to Pediatrics (UNIFESP), undergraduate in Nutrition (UFBA)

Dra. Sanjay Kinra; sanjay.kinra@lshtm.ac.uk

PhD in Epidemiology (University of Bristol), MFPHM in Public Health Medicine (Royal College of Physicians UK), MSc in Epidemiology (LSHTM, London), MD in Pediatrics (University of Delhi), MBBS in Medicine & Surgery (University of Delhi)

Dra. Louise Potvin; louise.potvin@umontreal.ca

PhD in Community Health (University of Montreal), M.A. Psychology (Concordia University, Montreal), member of the Steering Committee, principal investigator in the CIHR Centre Léa-Roback team.

Correspondence to:

Dra. Priscila Ribas de Farias Costa; prfarias@ufba.br;

PhD in Public Health (ISC/UFBA) with sandwich internship at LSHTM (University of London), MSc in Food, Nutrition and Health (ENUFBA), undergraduate in Nutrition (UFBA).

ABSTRACT

Introduction Micronutrient deficiencies are common in developing countries and are usually related to inadequate food intake, poor diet quality, and low bioavailability. Copper, selenium and zinc are essential minerals in several enzymatic reactions and their deficiencies are associated with worse prognosis in pregnancy, compromising maternal health as well as her offspring. Thus, the objective of the present systematic review will be to describe the prevalence of copper, selenium and zinc deficiencies in women of childbearing age.

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Strengths and limitations of this study:

- First systematic review that will assess the prevalence of copper, selenium and zinc deficiencies in women of childbearing age worldwide.
- A thorough and highly sensitive search strategy in leading databases, with no geographic or language restrictions, will be conducted by a multidisciplinary team with experience in systematic review.
- Different cut-off points.

- Heterogeneity among studies.

BACKGROUND:

Micronutrient deficiencies are common in many developing countries and are usually related to inadequate food intake, poor diet quality, low bioavailability (due to the presence of inhibitors, preparation mode and interactions) and/or the presence of infections, and are of growing public health concern[1,2]. Although the focus of discussions on micronutrient deficiency is around three main problems-vitamin A deficiency (VAD), iodine deficiency disorders (IDD), and iron deficiency anemia (IDA)-with higher prevalences in low-income settings, zinc, selenium, and copper deficiencies have stood out as a cause for concern worldwide, regardless of socioeconomic status[2,3]. Copper, selenium and zinc are essential minerals in several enzymatic reactions and their deficiencies may be associated with worse prognosis in pregnancy. Deficiencies may increase the risk of premature labor. But there are still contradictions[4–6].

Considering women of childbearing age, the consequences of deficiencies of these micronutrients can affect not only these individuals, but also their offspring. These women are susceptible to maternal and fetal deficiencies, affecting future generations[7]. The developmental period in utero is critical for the health of the child, both at birth and long after. Micronutrient deficiencies in women of childbearing age can be exacerbated during pregnancy, increasing the risk of maternal and child complications[2]. Maternal exposure to environmental hazards during pregnancy can therefore have a major impact on child health[8].

Thus, knowing the global, regional, and national prevalence of these nutritional deficiencies and their social determinants is of fundamental importance for planning policies and programs aimed at women's health in order to reduce the incidence of diseases associated with micronutrient deficiencies, as well as possible negative outcomes in pregnant women and infants.

Question formulation: What is the prevalence of copper, selenium and zinc deficiencies in women of childbearing age?

METHODS AND ANALYSIS

Search strategy

This is the protocol of a systematic review with meta-analysis to identify the global, regional and national prevalence of zinc, selenium and copper deficiencies in women of childbearing age. The study will be developed based on the recommendations of the JBI Manual for Evidence Synthesis[9] and written based on PRISMA-P (Preferred Reporting Items for

Systematic Reviews and Meta-Analyses Protocol)[10] and the protocol has been registered in the International Prospective Register of Systematic Reviews (PROSPERO)[11].

The search will be performed by two independent reviewers (T.C.C and J.C.D.P) and a third reviewer (P.R.F.C.) will be consulted in case of disagreement. The controlled terms will be searched on the MeSH, Decs and ENTREE platforms. The search will be done in PubMed/MEDLINE, Science direct, LILACS, ADOLEC, Scopus, EMBASE, CINAHL, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), Index Medicus for the South-East Asia Region (IMSEAR), Pan American Health Organization (PAHOS), Index Medicus for the Western Pacific (WPRIM), Index Medicus of the Eastern Mediterranean (IMEMR) and African Index Medicus (AIM). In order to saturate the searches, manual searches will be conducted with analysis of reference lists of included articles and relevant reviews, contact with authors of included studies, study registries and grey literature in OpenGrey and OVID platforms. For national data approach, results of CAPES theses and dissertations and the Digital Library of Theses and Dissertations (BDTD) will be searched. A first search will be performed and a second search will be performed just before submission.

Inclusion criteria for study designs

Observational cohort or cross-sectional studies and intervention studies with data on micronutrient deficiency before the intervention and with women of childbearing age as the population group will be included. Although most studies consider fertile age 15 to 49 years[12–14]. In this study, this group will be 10 and 49 years old, by request of the Brazilian Ministry of Health.

Studies in which participants were supplemented with micronutrients (copper, selenium, and zinc) or studies in which participants were selected because they belonged to a group with chronic or high-risk diseases will be excluded. Due to inability to calculate prevalence, case-control articles will also be excluded. Review studies and case reports, in vitro and in vivo studies, book chapters, and any other studies that did not assess prevalence or provide data for possible calculations will also be excluded. There will be no limitations related to language or year of publication, and no search filters will be used.

Qualitative and quantitative studies will be searched, with no date limits, language of publication, or search filter. Search strategies will be developed by a Health Sciences Librarian with experience in systematic reviews. Every strategy will be developed with input from the project. An outline of the search strategy for all bases is provided in the supplementary file.

Study selection

The entire search process will be exported to the Rayyan software (Rayyan QCRI/ web app), initiating the screening stage. Duplicate publications will be excluded to reduce the risk of bias. After this step, we will start reading the title and abstract to select the eligible publications (step I). Studies meeting the criteria will be directed to full-text reading (step II); if necessary, reviewers will contact study authors to obtain additional information to help make the decision about study inclusion in the review. After reading the full text, only studies that meet the pre-established eligibility criteria will be selected. All these steps will be performed by two independent reviewers (T.C.C. and J.C.D.P.) and a third reviewer (P.R.F.C.) will be consulted in case of disagreement.

A flowchart will be prepared accounting for the total number of articles found in the search, selected for screening, eligible for reading in full, included and excluded from the review. After reading in full, all articles that do not meet the eligibility criteria will be excluded and the reasons for this decision will be reported in a spreadsheet to compose the flowchart of study selection. In the manual search, the reference lists of the included articles will be examined, as well as the reviews on the topic, and the team will decide together which studies will be selected for synthesis and data extraction.

Data extraction and data items

After reading and selecting the included articles, data synthesis and extraction will begin. The entire process will be documented in Microsoft Excel software. The information collected will be study identification, study characteristics, participant characteristics, diagnosis and classification of the condition, prevalence, incidence and factors associated with the condition, as presented in table 1.

Table 1 - Information collection

Identification of the study	Title, first author's last name, year of publication, journal, volume, number and pages.
Study characteristics	Participant recruitment period, country, region, study design, study site, study

	setting, sampling process, data collection time, sample size.
Participant Characteristics	Information on study inclusion and exclusion criteria, mean/median age, ethnicity, proportion of participants with any therapy.
Diagnosis and classification of the condition	Measurement or diagnostic criteria used to define the condition (micronutrient deficiency), micronutrient evaluated, unit of measurement, cut-off point adopted.
Prevalence and incidence	Number of participants, total person follow-up time, number of cases of the condition, reported etiologies, prevalence, incidence rate, and their respective confidence intervals and/or p-value.

In the absence of necessary information, the team will contact the authors of the study (maximum of three attempts by e-mail), and the entire process will be documented and logged. The identification of duplicate, overlapping, or complementary articles (multiple articles from the same study) will be performed by identifying the registration numbers of the clinical trials, the authors' names, the city and location of the study (institutions, schools, hospitals, etc.), specific details of the study methodology, date and duration of the study (when applicable). If questions remain, the authors of the articles will be contacted.

Every extraction step will be performed by two previously trained reviewers. Legends will be elaborated with the objective of simplifying the data extraction spreadsheet.

Outcome assessment

The main outcome of this review is the identification of the global, regional (by continent) and national prevalence of zinc, selenium and copper deficiencies in women of childbearing age. These results can serve as a reference for the production of other works in the area, besides making public relevant data on women's health worldwide, supporting citations of this content by other

authors, thus increasing the visibility of scientific production and contributing to the knowledge about the deficiency of these micronutrients in the target audience.

Risk of bias assessment strategy

The evaluation of the risk of bias will be performed using the critical appraisal checklist for prevalence studies[9]. This checklist contains 9 items of questions regarding the sample, data collection, and statistical procedures used in the study. The response options are "yes", "no", "unclear" or "not applicable". The Newcastle-Ottawa scale will be used to evaluate the methodological quality[15].

All studies, regardless of their quality score, will be included in this review and the sensitivity analysis will assess the relevance of methodological quality in the final result. Both steps will be performed independently by two experienced and trained reviewers, and in case of disagreement a third reviewer will break the tie.

Analysis, data synthesis, publication bias and reporting

From these extracted data, a qualitative synthesis will be carried out structured around the prevalence of the deficiencies/inabilities identified in the studies, measurement units and cutoff points adopted, evaluating these results by country and socioeconomic situation (low, lower-middle, upper-middle, and high income countries).

For combinatorial studies[16], quantitative synthesis of data will be performed using meta-analysis. The extent of heterogeneity of the meta-analysis will be tested using Cochran's Q test and quantified by the inconsistency test (I^2 statistic). This statistic determines the magnitude of heterogeneity by the proportion of the total variation between studies due to heterogeneity[16]. A p-value is often cited as an indication of the extent of variability between studies. Therefore, the chi-square test will be employed to assess the significance of heterogeneity. A significance level of p-value <0.10 will be used to detect true heterogeneity among study results[16].

The magnitude of heterogeneity will be identified by calculating I^2, which ranges from 0 to 100%. Thus, I^2 close to zero suggests that all the dispersion can be attributed to the random error of the study, i.e., there is no heterogeneity. If an I^2 value close to 25% is calculated, it indicates low heterogeneity among studies; higher than 50% indicates moderate heterogeneity; and, above 75%, high heterogeneity[16].

In the presence of high heterogeneity, meta-analysis will be performed using the random effects model conducted with Stata's metaprop command. It allows the computation of 95% confidence intervals using the score statistic and the exact binomial method, as well as incorporating FreemanTukey's double-sine-arc transformation of proportions. This method also allows you to model intra-study variability using the binomial distribution. That is, it makes the data distribution normal and stabilizes variances[17]. The inverse function of the double sine-arc transformation has also been derived in the literature to recover the original proportion scale after data aggregation[17] while maintaining the interpretability of the final result. Thus, we will generate the summary prevalence for each outcome, as well as its respective 95% confidence interval, presented in Forest plot figures.

Potential variables that may influence the high heterogeneity among studies will be investigated by means of subgroup analysis (for dichotomous variables: age group, ethnicity, socioeconomic status, dosage form [blood or serum], cutoff point adopted, and anthropometric status) and meta-regression (for continuous variables: mean age, sample size, and mean BMI).

If ten or more studies are included in the meta-analysis, Egger's test and the funnel plot will be adopted to assess publication bias. In the funnel plot, the graphic funnel shape makes a qualitative assessment of the possibility of bias, in which asymmetries indicate the presence of publication bias. Egger's test will be applied when the variables are dichotomous or when the distribution of effects is normal (continuous variables); otherwise (asymmetric distribution), Begg's test will be applied. A strong probability that the distribution is not by chance, i.e., presence of publication bias, is suggested when p value <0.05[16].

Ethics, dissemination data protection

Ethical approval was not obtained since the data to be collected and analyzed cannot be linked to specific individuals.

Patient and public involvement

Since this will be a systematic review, there will be no direct patient or public involvement.

Ethics and dissemination

This systematic review will allow the identification of the prevalence of copper, selenium and zinc deficiencies in women of childbearing age at the global, regional and national (Brazil)

levels and will serve as a reference for the production of other works in the area, besides making public relevant data on women's health in Brazil and in the world, supporting citations of this content by other authors, thus increasing the visibility of the national scientific production and the Brazilian contribution to the world scientific knowledge.

Our dissemination strategy will involve the presentation in scientific meetings, as well as the publication of article(s) in international journals, peer-reviewed and open access, preparation of posters and oral presentations in Congresses and scientific events at national and international level, in the areas of nutrition and public health.

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Competing interests: This research has no conflict of interest.

Patient consent for publication: Not required.

Word Count: 2.813

REFERENCES

1. Ramakrishnan U, Ph D. Prevalence of Micronutrient Malnutrition Worldwide. *Nutr Rev*. 2002;(May):S46–S52. doi:https://doi-org.eres.qnl.qa/10.1301/00296640260130731
2. Pobee RA, Aguree S, Komeley Colecraft E, Gernand AD, Murray-Kolb LE. Food Insecurity and Micronutrient Status among Ghanaian Women Planning to Become Pregnant. Published online 2020. doi:10.3390/nu12020470
3. Magee, Pamela J; McCann MT. Conference on ' Targeted approaches to tackling current nutritional issues ' Micronutrient de fi ciencies : current issues. *Proceeding of the Nutrition Society*. Published online 2018:147-149. doi:10.1017/S0029665118002677
4. Monangi N, Xu H, Khanam R, et al. Association of maternal prenatal selenium concentration and preterm birth: a multicountry meta-analysis. *BMJ Glob Health*. 2021;6(9):e005856. doi:10.1136/BMJGH-2021-005856
5. Barman M, Brantsæter AL, Nilsson S, et al. Maternal dietary selenium intake is associated with increased gestational length and decreased risk of preterm delivery. *British Journal of Nutrition*. 2020;123(2):209-219. doi:10.1017/S0007114519002113
6. Zhang X, Feng YJ, Li J, et al. Maternal selenium deficiency during gestation is positively associated with the risks for LBW and SGA newborns in a Chinese population. *Eur J Clin Nutr*. 2021;75(5):768-774. doi:10.1038/s41430-020-00809-x
7. Panth P, Guerin G, DiMarco NM. A Review of Iodine Status of Women of Reproductive Age in the USA. *Biol Trace Elem Res*. 2019;188(1):208-220. doi:10.1007/s12011-018-1606-5
8. Simpson JOEL, Bailey LB, Pietrzik K, Shane B, Holzgreve W. Micronutrients and women of reproductive potential : required dietary intake and consequences of dietary deficiency or excess . Part I – Folate , Vitamin B12 , Vitamin B6. 2010;23(December):1323-1343. doi:10.3109/14767051003678234
9. Aromataris E MZ. JBI Manual for Evidence Synthesis. doi:https://doi.org/10.46658/JBIMES-20-01
10. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Revista Espanola de Nutricion Humana y Dietetica*. 2016;20(2):148-160. doi:10.1186/2046-4053-4-1
11. Ribas De Farias Costa P, Santana L, Potvin L, et al. *PROSPERO*. Accessed June 30, 2022. https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=165352
12. Stevens GA, Beal T, Mbuya MNN, et al. Micronutrient deficiencies among preschool-aged children and women of reproductive age worldwide: a pooled analysis of individual-level data from population-representative surveys. *Lancet Glob Health*. 2022;10(11):e1590-e1599. doi:10.1016/S2214-109X(22)00367-9

13. Gupta S, Brazier AKM, Lowe NM. Zinc deficiency in low- and middle-income countries: prevalence and approaches for mitigation. *Journal of Human Nutrition and Dietetics*. 2020;33(5):624-643. doi:10.1111/jhn.12791

14. Belay A, Gashu D, Joy EJM, et al. Mineral micronutrient status and spatial distribution among the Ethiopian population. doi:10.1017/S0007114522000319

15. Munn Z, MClinSc SM, Lisy K, Riitano D, Tufanaru C. Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data. *Int J Evid Based Healthc*. 2015;13(3):147-153. doi:10.1097/XEB.0000000000000054

16. Higgins J, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions. version 6.3. Published 2022. Accessed July 3, 2021. www.training.cochrane.org/handbook

17. Jeong J hyeon. Domain of Inverse Double Arcsine Transformation. 2018;1(1):2-5.

Full Search Strategy

PUBMED

The advanced search will be performed on the pubmed platform. In the first step, synonymous terms will be entered for exposure and separately for each outcome using the Boolean operators OR and performed the search for isolated variables.

#1 (Childbearing age) OR (Reproductive Age) OR (Age, Reproductive)
#2 (Copper) OR (Copper status)
#3 (Selenium) OR (Selenium status)
#4 (Zinc) OR (Zinc status)

The search will be performed using the Boolean operator AND between the independent and dependent variables. No filter will be used to perform the search.

(Childbearing age) OR (Reproductive Age) OR (Age, Reproductive) AND (Copper) OR (Copper status)
(Childbearing age) OR (Reproductive Age) OR (Age, Reproductive) AND (Selenium) OR (Selenium status)
(Childbearing age) OR (Reproductive Age) OR (Age, Reproductive) AND (Zinc) OR (Zinc status)

SCIENCE DIRECT
childbearing or reproductive age or age,reproductive AND ZINC
childbearing or reproductive age or age,reproductive AND COPPER
childbearing or reproductive age or age,reproductive AND SELENIUM

LILACS - By BVS filter
(women OR women's health) AND zinc
(women OR women's health) AND copper
(women OR women's health) AND selenium

ADOLEc - By BVS filter
(women OR women's health) AND zinc
(women OR women's health) AND copper
(women OR women's health) AND selenium

SCOPUS
#1 “Childbearing age” OR “Reproductive Age” OR “Age, Reproductive”
#2 “Copper”OR “Copper status”
#3 “Selenium” OR “Selenium status”
#4 “Zinc” OR “Zinc status”

“Childbearing age” OR “Reproductive Age” OR “Age, Reproductive” AND “Copper”OR “Copper status”

"Childbearing age" OR "Reproductive Age" OR "Age, Reproductive" AND "Selenium" OR "Selenium status"
"Childbearing age" OR "Reproductive Age" OR "Age, Reproductive" AND "Zinc" OR "Zinc status"

EMBASE
#1 'childbearing age'/exp OR 'childbearing age' OR (('childbearing'/exp OR childbearing) AND ('age'/exp OR age))
#2 'reproductive age'/exp OR 'reproductive age'
#3 'copper'/exp OR copper
#4 'copper status' OR (('copper'/exp OR copper) AND status)
#5 'selenium'/exp OR selenium
#6 'selenium status' OR (('selenium'/exp OR selenium) AND status)
#7 'zinc'/exp OR zinc
#8 'zinc status' OR (('zinc'/exp OR zinc) AND status)

#9 - combination #1 OR #2
('childbearing age'/exp OR 'childbearing age' OR (('childbearing'/exp OR childbearing) AND ('age'/exp OR age))) OR ('reproductive age'/exp OR 'reproductive age')

#10 – combination #3 OR #4
('copper'/exp OR copper) OR ('copper status' OR (('copper'/exp OR copper) AND status))

#11 – combination #5 OR #6
('selenium'/exp OR selenium) OR ('selenium status' OR (('selenium'/exp OR selenium) AND status))

#12 – combination #7 OR #8
('zinc'/exp OR zinc) OR ('zinc status' OR (('zinc'/exp OR zinc) AND status))

#13 – combination #9 OR #10
(('childbearing age'/exp OR 'childbearing age' OR (('childbearing'/exp OR childbearing) AND ('age'/exp OR age))) OR ('reproductive age'/exp OR 'reproductive age')) OR (('copper'/exp OR copper) OR ('copper status' OR (('copper'/exp OR copper) AND status)))

#14 – combination #9 OR #11
(('childbearing age'/exp OR 'childbearing age' OR (('childbearing'/exp OR childbearing) AND ('age'/exp OR age))) OR ('reproductive age'/exp OR 'reproductive age')) OR (('selenium'/exp OR selenium) OR ('selenium status' OR (('selenium'/exp OR selenium) AND status)))

#15 - combination #9 OR #12
(('childbearing age'/exp OR 'childbearing age' OR (('childbearing'/exp OR childbearing) AND ('age'/exp OR age))) OR ('reproductive age'/exp OR 'reproductive age')) OR (('zinc'/exp OR zinc) OR ('zinc status' OR (('zinc'/exp OR zinc) AND status)))

CINAHL

#1 (Childbearing age) OR (Reproductive Age) OR (Age, Reproductive)
#2 (Copper) OR (Copper status)
#3 (Selenium) OR (Selenium status)
#4 (Zinc) OR (Zinc status)

(Childbearing age) OR (Reproductive Age) OR (Age, Reproductive) AND (Copper) OR (Copper status)
(Childbearing age) OR (Reproductive Age) OR (Age, Reproductive) AND (Selenium) OR (Selenium status)
(Childbearing age) OR (Reproductive Age) OR (Age, Reproductive) AND (Zinc) OR (Zinc status)

WEB OF SCIENCE

1 TS= ((Childbearing age) OR (Reproductive Age) OR (Age, Reproductive))
#2 TS= ((Copper) OR (Copper status))
#3 TS= ((Selenium) OR (Selenium status))
#4 TS= ((Zinc) OR (Zinc status))

((Childbearing age) OR (Reproductive Age) OR (Age, Reproductive)) AND ((Copper) OR (Copper status))
((Childbearing age) OR (Reproductive Age) OR (Age, Reproductive)) AND ((Selenium) OR (Selenium status))
((Childbearing age) OR (Reproductive Age) OR (Age, Reproductive)) AND ((Zinc) OR (Zinc status))

COCHRANE LIBRARY

#1 (Childbearing age) OR (Reproductive Age) OR (Age, Reproductive)
#2 (Copper) OR (Copper status)
#3 (Selenium) OR (Selenium status)
#4 (Zinc) OR (Zinc status)

(Childbearing age) OR (Reproductive Age) OR (Age, Reproductive) AND (Copper) OR (Copper status)
(Childbearing age) OR (Reproductive Age) OR (Age, Reproductive) AND (Selenium) OR (Selenium status)
(Childbearing age) OR (Reproductive Age) OR (Age, Reproductive) AND (Zinc) OR (Zinc status)

OPEN GREY

"childbearing" and copper
"childbearing" and zinc
"childbearing" and selenium
“reproductive age” and copper

"reproductive age" and zinc
"reproductive age" and selenium
“age, reproductive” and copper
"age, reproductive" and zinc
"age, reproductive" and selenium

IMSEAR - Index Medicus for the South-East Asia Region - By BVS filter
(women OR women's health) AND zinc
(women OR women's health) AND copper
(women OR women's health) AND selenium

PAHOS IRIS - Pan American Health Organization - By BVS filter
(women OR women's health) AND zinc
(women OR women's health) AND copper
(women OR women's health) AND selenium

WPRIM - Index Medicus for the Western Pacific - By BVS filter

(women OR women's health) AND zinc
(women OR women's health) AND copper
(women OR women's health) AND selenium

IMEMR - Index Medicus of the Eastern Mediterranean - By BVS filter
(women OR women's health) AND zinc
(women OR women's health) AND copper
(women OR women's health) AND selenium

BDTD - THESES AND DISSERTATIONS CATALOG - access through the CAPES platform
"women" OR women's health AND "zinc"
"women" OR women's health AND "copper"
"women" OR women's health AND "selenium"

No filter was used on any platform.

Reporting checklist for protocol of a systematic review and meta analysis.

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-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	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	1
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1

Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	10
Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support			
Sources	#5a	Indicate sources of financial or other support for the review	10
Sponsor	#5b	Provide name for the review funder and / or sponsor	10
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	10
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	4
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
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	4-5
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	5
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	5

Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6
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)	6-7
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	6-7
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	6-7
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6-7
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	8
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)	8
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	9
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9

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