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

Priscila Ribas Costa ,[1,2] Thais Carvalho,[1] Jacqueline Costa Dias Pitangueira,[1,3] Mônica Leila Portela Santana,[1,2] Sanjay Kinra,[4] Louise Potvin[5]

To cite: Costa PR, Carvalho T, Pitangueira JCD, *et al*. Global, regional and national prevalence of copper, selenium and zinc deficiencies in women of childbearing age: protocol for systematic review and meta-analysis. *BMJ Open* 2023;**13**:e066324. doi:10.1136/bmjopen-2022-066324

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-066324).

Received 21 July 2022
Accepted 09 February 2023

For numbered affiliations see end of article.

Correspondence to
Dr Priscila Ribas Costa; prfarias@ufba.br

ABSTRACT

Introduction Micronutrient deficiencies are common in low-income and middle-income 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.

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. A first search will be performed and a second search will be performed just before submission. 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.

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 geographical 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 low-income and middle-income 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, iodine-deficiency disorders and iron-deficiency anaemia 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 labour. 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 programmes 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 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 (TC and JCDP) and a third reviewer (PRC) 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 15–49 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 online supplemental file 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 (TC and JCDP) and a third reviewer (PRC) will be consulted in case of disagreement.

A flow chart 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 flow chart 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.

In the absence of necessary information, the team will contact the authors of the study (maximum of three attempts by email), and the entire process will be

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	No of participants, total person follow-up time, no of cases of the condition, reported aetiologies, prevalence, incidence rate and their respective CIs and/or p value.

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 nine 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 cut-off 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 χ^2 test will be employed to assess the significance of heterogeneity. A significance level of $p<0.10$ 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 closes to zero suggests that all the dispersion can be attributed to the random error of the study, that is, there is no heterogeneity. If an I^2 value closes 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% CIs using the score statistic and the exact binomial method, as well as incorporating Freeman-Tukey's double-sine-arc transformation of proportions. This method also allows you to model intrastudy variability using the binomial distribution. That is, it makes the data distribution normal and stabilises 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% CI, 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), cut-off point adopted and anthropometric status) and meta-regression (for continuous variables: mean age, sample size and mean body mass index).

If 10 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, that is, presence of publication bias, is suggested when $p<0.05$.[16]

Ethics, dissemination data protection

Ethical approval was not obtained since the data to be collected and analysed 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.

Author affiliations
[1]Universidade Federal da Bahia Escola de Nutrição, Salvador, Bahia, Brazil
[2]Departamento de ciências da nutrição, Universidade Federal da Bahia, Salvador, Bahia, Brazil
[3]Departamento de práticas de cuidado em nutrição, Universidade Federal do Recôncavo da Bahia, Santo Antônio de Jesus, Bahia, Brazil
[4]Departament of non communicable disease epidemiology, London School of Hygiene And Tropical Medicine, London, UK
[5]Departament of social and preventive medicine, University of Montreal, Montréal, UK

Acknowledgements We would like to thank the whole NUBASE team for all the support in the elaboration of this project.

Contributors PRC supervised the study and contributed to study conception, design and manuscript drafting. TC contributed to study conception, design and manuscript drafting. JCDP contributed to study conception, design and manuscript drafting. MLPS contributed to study conception, design and manuscript drafting. SK contributed to study conception, design and manuscript drafting. LP contributed to study conception, design and manuscript drafting. All authors critically reviewed and approved the final manuscript for submission.

Funding This work was supported by the research promotion foundation CNPq, Call MS-SCTIE-Decit/CNPq No 26/2019—Research in Food and Nutrition. Funders are not directly involved in project.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD
Priscila Ribas Costa http://orcid.org/0000-0003-3809-9037

REFERENCES

1 Ramakrishnan U. Prevalence of micronutrient malnutrition worldwide. *Nutr Rev* 2002;60:S46–52.
2 Pobee RA, Aguree S, Colecraft EK, *et al*. Food insecurity and micronutrient status among Ghanaian women planning to become pregnant. *Nutrients* 2020;12:470.
3 Magee PJ, McCann MT. Conference on 'targeted approaches to tackling current nutritional issues' micronutrient de fi ciencies: current issues. *Proceeding of the Nutrition Society* 2018:147–9.
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:e005856.
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. *Br J Nutr* 2020;123:209–19.
6 Zhang X, Feng Y-J, 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;75:768–74.
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;188:208–20.
8 Simpson J, Bailey LB, Pietrzik K, *et al*. Micronutrients and women of reproductive potential: required dietary intake and consequences of dietary deficiency or excess. Part I -- folate, vitamin B12, vitamin B6. *J Matern Fetal Neonatal Med* 2010;23:1323–43.
9 Aromataris E, Munn Z. JBI manual for evidence synthesis. 2020.
10 Moher D, Shamseer L, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.
11 Ribas De Farias Costa P, Santana L, Potvin L, *et al*. PROSPERO. Available: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=165352 [Accessed 30 Jun 2022].
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:e1590–9.
13 Gupta S, Brazier AKM, Lowe NM. Zinc deficiency in low- and middle-income countries: prevalence and approaches for mitigation. *J Hum Nutr Diet* 2020;33:624–43.
14 Belay A, Gashu D, Joy EJM, *et al*. Mineral micronutrient status and spatial distribution among the Ethiopian population. *Br J Nutr* 2022;128:2170–80.
15 Munn Z, Moola S, Lisy K, *et al*. Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data. *Int J Evid Based Healthc* 2015;13:147–53.
16 Higgins J, Thomas J, Chandler J, *et al*. Cochrane handbook for systematic reviews of interventions. version 6.3; 2022. Available: www.training.cochrane.org/handbook [Accessed 3 Jul 2021].

17 Jeong JH. Domain of inverse double arcsine transformation. *ArXiv* 2018;1:2–5.