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The association between selenium levels and hypertensive disorders of pregnancy: a systematic review of the literature

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Abstract

Selenium (Se) is essential for selenoprotein synthesis, being thus important for immune and thyroid function, and for antioxidant defence. Some studies have shown that low levels of Se may associate with hypertensive disorders of pregnancy (HDP). Nevertheless, evidence supporting Se supplementation in pregnant or childbearing-age women is still lacking. In this context, this work aimed to systematically review the most recent scientific evidence to understand the relationship between Se levels and HDP. We performed a systematic review (protocol number: CRD42022310424) with literature of the last decade. PubMed, Scopus, Web of Science, registers and grey literature were searched to identify studies reporting measurement of Se levels in normotensive and hypertensive pregnant women (supplemented or not with Se). Study quality was assessed using the National Heart, Lung, and Blood Institute Study Quality Assessment Tools. Among the thirty included studies, a majority, 61 % (*n* 19) of the 'good' or 'fair' studies, reported a negative association between Se and HDP, and some studies, 39 % (*n* 11) of the 'good' or 'fair' studies, reported a lack of association. This review provides an important amount of quality evidence suggesting that low Se levels associate with the occurrence of HDP. Nevertheless, the gathered information is not enough to underlie a recommendation for Se supplementation in pregnancy to protect against HDP. Thus, this review emphasises the need for further well-designed randomised controlled trials that may provide blunt evidence regarding the benefits of Se supplementation during pregnancy.

Key words: Selenium: Pregnancy: Hypertensive disorders of pregnancy: Pregnancy-induced hypertension: Gestational hypertension: Pre-eclampsia: Eclampsia

Essential trace elements, such as Fe, Cu, I, Zn and Se, are dietary elements that occur in a very small portion in the human body (usually less than 1–10 parts per million) and play significant roles in the development, growth and appropriate function of cells. These elements are involved as cofactors in enzyme catalysis, being essential for a plethora of biological mechanisms and functions, including reproduction[1].

Se is particularly important due to its anti-inflammatory, chemopreventive and antiviral characteristics[2,3]. In addition, this element plays an important role in neutralising oxidative stress since it is an integral part of several selenoproteins such as glutathione peroxidase and thioredoxin reductase. The majority of all known selenoproteins are expressed in the thyroid gland[4]. In fact, it is known that Se composes the enzyme iodothyronine deiodinase, which is important in thyroid hormone production, and it also composes other enzymes such as selenoproteins S, P and W[5].

Se is naturally found in meat, seafood, grains, seeds and nuts[6] and its food content can vary geographically, depending on the natural availability of Se in the soil and the direct addition of this element to the food supply[7]. The RDA of Se for adult men and women is 55 µg (0·7 µmol)/d[8]; however, this value can increase in certain conditions, namely in pregnancy, in which Se requirements are 65 µg/d[9].

In recent years, several studies have shown that low levels of Se may be involved in some adverse pregnancy conditions, such as gestational diabetes, miscarriages and premature birth[10,11]. Additionally, many authors associate lower levels of Se in placental tissue, blood or toenail with the decreased activity of glutathione peroxidase and, subsequently, with pregnancy-induced hypertension (PIH)[12,13].

The *International Society for the Study of Hypertension in Pregnancy* (ISSHP) divides the hypertensive disorders of pregnancy (HDP) into two categories: 'Hypertension known before pregnancy or present in the first 20 weeks' and 'Hypertension arising *de novo* at or after 20 weeks'[14]. Hypertension arising *de novo* at or after the 20th gestational week – which is the focus of this review – may be classified as: (a) transient gestational hypertension, when hypertension is detected in clinical setting and resolves with repeated blood pressure readings; (b)

Abbreviations HDP, hypertensive disorders of pregnancy; PE, pre-eclampsia; PIH, pregnancy-induced hypertension; RCT, randomised controlled trial.

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gestational hypertension (the above referred PIH), if there is not any specific sign of pre-eclampsia (PE) (e.g. proteinuria); (c) *De novo* PE and (d) PE superimposed on chronic hypertension. In all cases, the ISSHP defines hypertension as a systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, based on an average of at least two measurements.

There are some clinical papers demonstrating potential benefits of Se supplementation during pregnancy for HDP's prevention; nevertheless, current evidence does not support yet the use of Se in pregnancy and women of childbearing age due to insufficient data and conflicting results[15]. In fact, there is no current comprehensive review that systematises the status of knowledge about this topic. So, this work aimed to systematically review the most recent scientific evidence to understand the relationship between Se levels and HDP. In addition, this review aims to provide a reflection on the potential effectiveness of using Se as a supplement during pregnancy to prevent HDP or as an adjuvant treatment for these conditions.

Methods

Design

This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[16].

The protocol of this study was registered in the International Prospective Register of Systematic Reviews (identifier: CRD42022310424), and it is available online in (https://www.crd.york.ac./prospero/display_record.php?IDuk=CRD42022310424).

Data sources, search strategy and eligibility criteria

For this systematic review, PubMed, Scopus and Web of Science databases were searched for relevant articles published in the last 10 years. Table 1 shows the terms used for database search (the same terms were used for the three databases). We chose to restrict our search on publication date since the last specific systematic review we found about this topic was published in 2016[17]. Additional data sources were used such as reference lists of retrieved publications, *grey literature* (Portuguese journals and public master's thesis and dissertations from the University of Porto) and the clinical trials databases *clinicaltrials.gov* and *European Union Clinical Trials Register*. The literature search was performed in December 2021, and the last update was conducted on February 2022.

Table 1. Search terms used in the database search

1	Pregnancy [MeSH]
2	Pregnancy [Text Word]
3	Pregnant women [MeSH]
4	Pregnant women [Text Word]
5	#1 OR #2 OR #3 OR #4
6	Selenium [MeSH]
7	Selenium [Text Word]
8	Selenium supplementation [Text Word]
9	#6 OR #7 OR #8
10	Hypertension, pregnancy-induced [MeSH]
11	Pregnancy-induced hypertension [Text Word]
12	Pre-Eclampsia [MeSH]
13	Pre-Eclampsia [Text Word]
14	Preeclampsia [Text Word]
15	Eclampsia [MeSH]
16	Eclampsia [Text Word]
17	HELLP syndrome [MeSH]
18	HELLP syndrome [Text Word]
19	#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18
20	# 5 AND #9 AND # 19

The primary outcome of this revision was the occurrence of HDP. Additionally, the use of Se supplements was considered as a secondary outcome. Studies were included whenever they referred to: (1) the population of interest, that is, pregnant women; (2) the exposure of interest, that is, measurement of Se levels in any biological sample regardless of Se supplementation at any dose, regimen and type (e.g. Se-only supplements or Se as part of multivitamin/mineral tablets); (3) the outcome of interest, that is, the prevalence or development of HDP and (4) any of the following study types: observational, nonrandomised experimental studies and randomised controlled trials (RCT).

We excluded: animal and *in vitro* studies; studies in languages other than English, Portuguese, Italian, Spanish or French; unpublished or non-peer-reviewed articles; case reports; narrative reviews/comment articles; systematic reviews and meta-analyses.

Study selection and data extraction

The reference management software *EndNote X20* was used to remove duplicate studies and to organise the resulting aggregated database. Titles and abstracts were independently screened by two reviewers (EK and IS). Studies in which the abstract did not mention the outcome of interest were automatically excluded and disagreements between reviewers, which was very low, were resolved through discussion.

The full texts of the potentially eligible studies were assessed for inclusion by two review team members (EK and IS) and discrepancies were resolved by consensus between the whole group. Afterwards, thirty articles were considered to include in the current revision. A flow chart of the study selection process can be found in Fig. 1. After the inclusion phase, relevant information about studies was extracted by three reviewers with an overlap of five studies, for assessment of study quality and evidence synthesis. Data extraction included: reference details (first author name, publication year of study); study details (study type, country); participant details (study population, inclusion and exclusion criteria of participants, number of participants); exposure details (biological sample, pregnancy timepoint and assay method for Se quantification) and main results of the study. Discrepancies were resolved by consensus between the three authors. The corresponding author of one of the included articles was contacted by email to clarify about the study type.

Quality assessment of included studies

Quality assessment of included studies was performed using the National Heart, Lung, and Blood Institute (NHLBI) Study Quality Assessment Tools. Three different tools were used depending on the study type. All authors independently assessed the quality with an overlap of ten articles for calibration of criteria

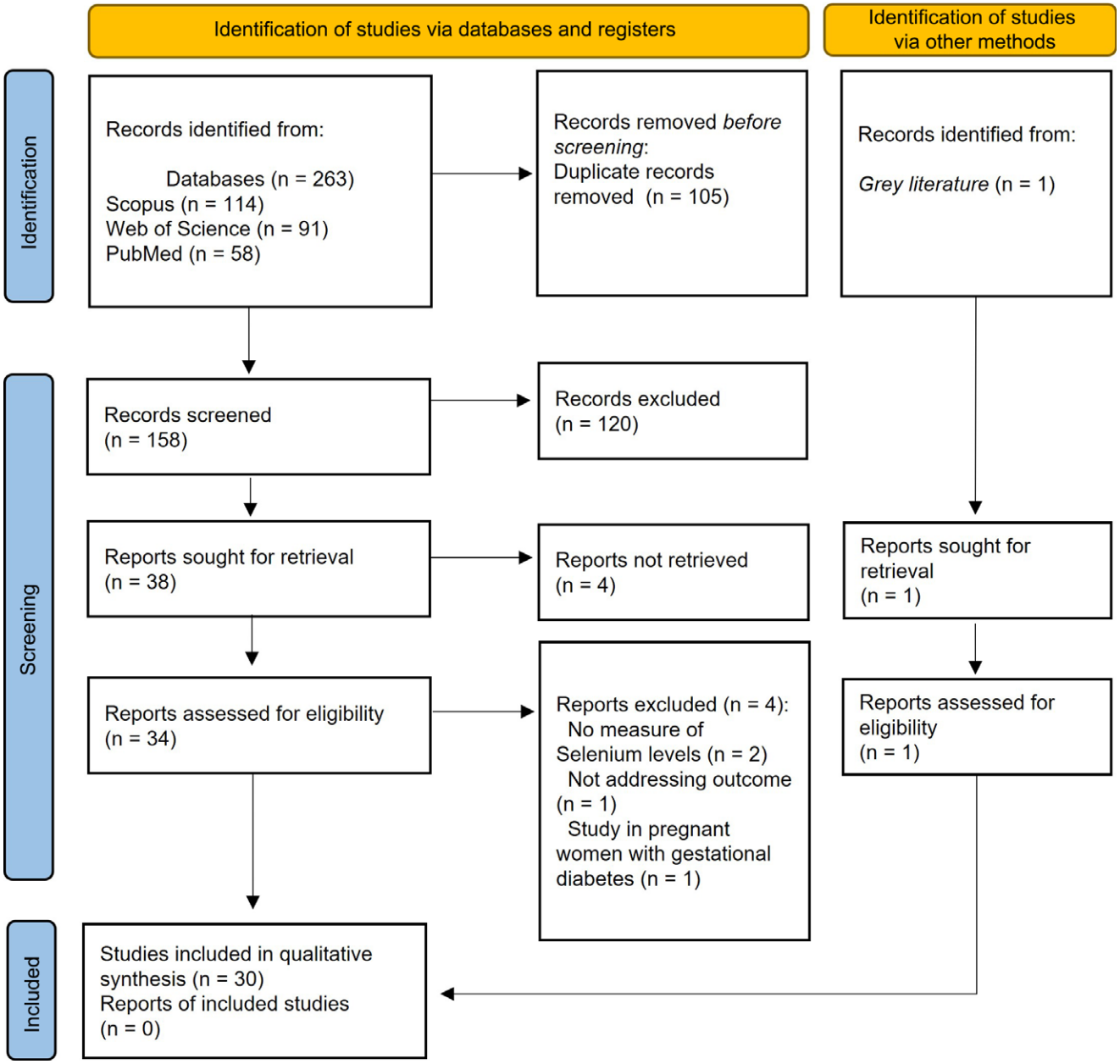

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart of study selection.

application. Each item of questionnaires was evaluated as 'Yes', 'No', 'Not Applicable', 'Cannot Determine' or 'Not Reported', according to NHLBI's instructions. In the end, an overall rating of 'Good', 'Fair' or 'Poor' quality was used based on the total score obtained for each article. Any disagreement between the authors was resolved through discussion. Results of quality assessment of all the studies are presented in online Supplementary Tables 1, 2 and 3.

Results

A total of 263 articles were identified from the three databases mentioned previously, and one dissertation was identified from grey literature. After combining the various databases, 105 duplicates were removed and 158 records were screened afterwards. Among these, 120 articles were excluded based on title and abstract considering the inclusion and exclusion criteria. The remaining thirty-eight articles were sought for full-text retrieval. Four full texts were unavailable and, so, thirty-four articles were screened for eligibility based on full text. Of these, four articles were excluded: two of them did not describe Se levels; one study did not address any of the outcomes of interest and one other referred to assessment of Se levels in pregnant women with gestational diabetes. The dissertation (from *grey literature*) was also excluded because it was a narrative review. As a result, thirty articles were included in the study. A flow chart of the article search, selection and screening can be found in Fig. 1.

General characteristics of included studies

Table 2 summarises general information about studies included in this review. Almost all the thirty included studies were observational (*n* 29), and the majority of them were case–control studies (77 %, *n* 23). Among the case–control studies, five were nested case–control studies[18,19,20,21,22] and one was a prospective case–control study[23]. A minority of the studies were prospective cohorts (*n* 3)[24,25,26], retrospective cohort (*n* 1)[27] or cross-sectional (*n* 2)[28,29]. Among the included studies, only one was an RCT[30].

Regarding geographical distribution, the included studies were performed in a total of seventeen countries from all over the world. Most studies were carried out in Asian population (33 %, *n* 10)[19,23,24,28,31,32,33,34,35,36], and the remaining articles are evenly distributed across Europe[25,26,30,37,38], Africa[39,40,41,42,43,44] and America[18,20,27,45,46]. An exception was Australia, which had only two studies[21,29], one of which a multicentre study[22] and one study was conducted in an European-Asian country[47]. Overall, the most represented countries were Iran, Nigeria and the USA, with three studies each.

Table 2. General information about studies included in this systematic review (numbers and percentages)

	Total number of studies (*n* 30)	
	n	%
Study type		
Case–control	23	77
Prospective cohort	3	10
Retrospective cohort	1	3
Cross-sectional	2	7
RCT	1	3
Publication year		
2017–2021	18	60
2012–2016	12	40
Continents and countries		
Asia (Iran, Iraq, Bangladesh, Israel, South Korea, India)	10	33
Oceania (Australia)	2	7
Europe (UK, Poland, Norway)	5	17
Africa (Nigeria, South Africa, DR Congo)	6	20
America (USA, Brazil)	5	17
Turkey	1	3
Multicentre study: Australia, New Zealand, UK	1	3
Timepoint/gestational age of Se levels measurement		
First, second and third trimester	1	3
First trimester only	2	6
Second trimester only	3	9
Third trimester only	14	44
Second and then in third trimester	2	6
Case group at third trimester and control group at second trimester	1	3
At delivery	5	16
After delivery	1	3
Unclear/not reported	3	9
Biological sample analysed		
Maternal serum/plasma/whole blood	24	75
Maternal urine	2	6
Maternal nail	2	6
Maternal hair	1	3
Placenta	1	3
Cord blood	2	6
Se quantification method		
Atomic absorption spectrophotometry (with no specification)	4	13
Graphite furnace atomic absorption spectrophotometry	4	13
Flame atomic absorption spectrophotometry	2	6
Inductively coupled plasma – mass spectrometry	17	55
Instrumental neutron activation analysis	2	6
Unclear/not reported	2	6
Assessment of Se intake		
No	28	93
Yes	2	7
Women supplemented with Se		
No	27	90
Yes	3	10
Overall study quality		
Poor	2	7
Fair	13	43
Good	15	50

RCT, randomised controlled trial.

In terms of period of exposure assessment, almost half of the studies (44 %, *n* 14) evaluated Se levels in a biological sample collected in the third trimester. Also, three other studies evaluated Se levels in the third trimester in addition to another previous timepoint evaluation[19,24,30]. Several studies (16 %, *n* 5) evaluated Se levels at delivery[23,34,36,37,42] and one study used samples collected within 24–72 h after delivery[27]. Importantly, three studies evaluated Se levels in the first trimester, that is, before the diagnosis of HDP (after 20 weeks) took place[24,26,38]. In three studies, it was not possible to obtain rigorous information about the period of exposure assessment[28,40,47].

Diverse biological samples were collected for analysis and some studies assessed more than one type of biological sample[23,30,42]. As it can be observed in Table 2, the great majority of studies (75 %, *n* 24) analysed maternal blood samples (serum, plasma or whole blood), followed by maternal urine (*n* 2)[18,39], nail (*n* 2)[30,44] and hair samples (*n* 1)[42]. Only one study used placenta[20] and two studies used cord blood samples[23,36].

Se was measured mainly using inductively coupled plasma – mass spectrometry (ICP-MS) (55 % of studies, *n* 17); however, some studies used different quantification methods, such as atomic absorption spectrometry (*n* 10) and instrumental neutron activation analysis (*n* 2). Two studies did not report the method used for Se quantification[28,36].

Although most studies have evaluated Se levels only in non-supplemented women, in three studies Se levels were measured in supplemented and non-supplemented pregnant women[28,29,30]. Furthermore, two studies evaluated Se intake through food frequency questionnaires (FFQ)[25,29].

Regarding quality assessment, 50 % (*n* 15) of studies were classified as 'Good'; 43 % (*n* 13) were classified as 'Fair' and 7 % (*n* 2) were classified as 'Poor'. 'Poor' classified studies are a case–control study[42] and a cross-sectional study[28].

Systematisations of the risk of bias for case–control studies and for observational cohort and cross-sectional studies included in this review are illustrated in Fig. 2 and 3, respectively.

Data from included studies

Results of data extraction from studies are systematised in Table 3 (case–control studies) and Table 4 (non-case–control studies). These tables also include the overall rating of quality for each study. Overall, the smallest population size was 44 women (34 PE cases and controls and 10 non-pregnant women)[37] and the largest sample size was 69 972 women (69 972 women for analysis of Se intake and 2572 of them were also assessed for Se status)[25]. Twenty-three studies reported PE as an outcome, six studies reported both PE and gestational hypertension as study outcomes[25,26,30,38,45,46] and one study reported PE and eclampsia[36].

Most studies excluded women with risk factors for HDP, such as twin pregnancy, overweight and obesity, history of hypertension and diabetes. Online Supplementary Table 4 describes in detail the inclusion and/or exclusion criteria of participants of each study.

Nineteen studies found a negative association between Se levels and the prevalence or development of HDP, and eleven studies did not find any association. None of the studies reported a positive association.

Negative association between Se and hypertensive disorders of pregnancy

All the nineteen studies that found a negative association between Se levels and the prevalence or development of HDP referred to PE; however, three of them also referred to gestational hypertension/PIH[26,30,38] and one to eclampsia[36]. Of the nineteen studies, sixteen refer to Se levels quantified in serum/plasma/blood, and regarding quality, eight were classified as 'Good'[18,19,21,26,30,38,40,41], nine were classified as 'Fair'[23,31,32,33,35,36,37,43,44] and two studies were classified as 'Poor'[28,42] (Tables 3 and 4).

In addition to data showing negative associations between Se and HDP, which details can be found in Tables 3 and 4, some other important conclusions were found. For example, Eze *et al.*[41] observed that maternal serum Se deficiency worsened with the increasing severity of PE ($P < 0{\cdot}001$).

In line with this, Haque *et al.*[33] reported that maternal serum Se concentrations for mild and severe PE were significantly different (24·63 (SD 0·65) μg/l and 21·71 (SD 1·35) μg/l, respectively) ($P < 0{\cdot}05$); Negi *et al.*[36] reported that cord blood Se concentrations were lower in the hypertension cases ($P < 0{\cdot}005$), and eclampsia cases tended to present lower values of Se in comparison with the PE cases and Soobramoney *et al.*[44] observed that, despite maternal nail Se levels were similar between PE and normotensive (NT) women ($P > 0{\cdot}05$), lower Se levels were significantly related to the severity of PE ($P < 0{\cdot}05$).

Importantly, Lewandowska *et al.*[26] found that lower Se levels in serum were found in pregnant women who subsequently developed gestational hypertension or PE, compared with matched controls who remained normotensive ($P < 0{\cdot}05$). Concurring with this, Lewandowska *et al.*[38] also reported that an increase in maternal serum Se concentrations of 1 μg/l reduced the risk of gestational hypertension/PE and isolated gestational hypertension by 5 % ($P = 0{\cdot}011$) and 6 % ($P = 0{\cdot}004$), respectively. In the same line of evidence, Bommarito *et al.*[18] reported that an interquartile range increase in urinary Se was associated with a reduction in the risk of PE (hazard ratio [HR]: 0·28, 95 % CI (0·08, 0·94)). Lastly, Rayman *et al.*[30], the only RCT included in this review, used samples originated from the SPRINT (Selenium in PRegnancy INTervention) study[48], in which primiparous women from UK were randomised to treatment with Se (60 mg/d) or placebo from 12 to 14 weeks of gestation until delivery. After exclusion of non-compliers with Se treatment, Se supplementation was found to significantly reduce the OR for gestational hypertension/PE (OR 0·30, 95 % CI (0·09, 1·00), $P = 0{\cdot}049$).

Lack of association between Se levels and hypertensive disorders of pregnancy

Eleven studies did not find any association between Se levels and HDP. Of these studies, nine refer to Se levels quantified in serum/plasma/blood and, regarding quality, seven were

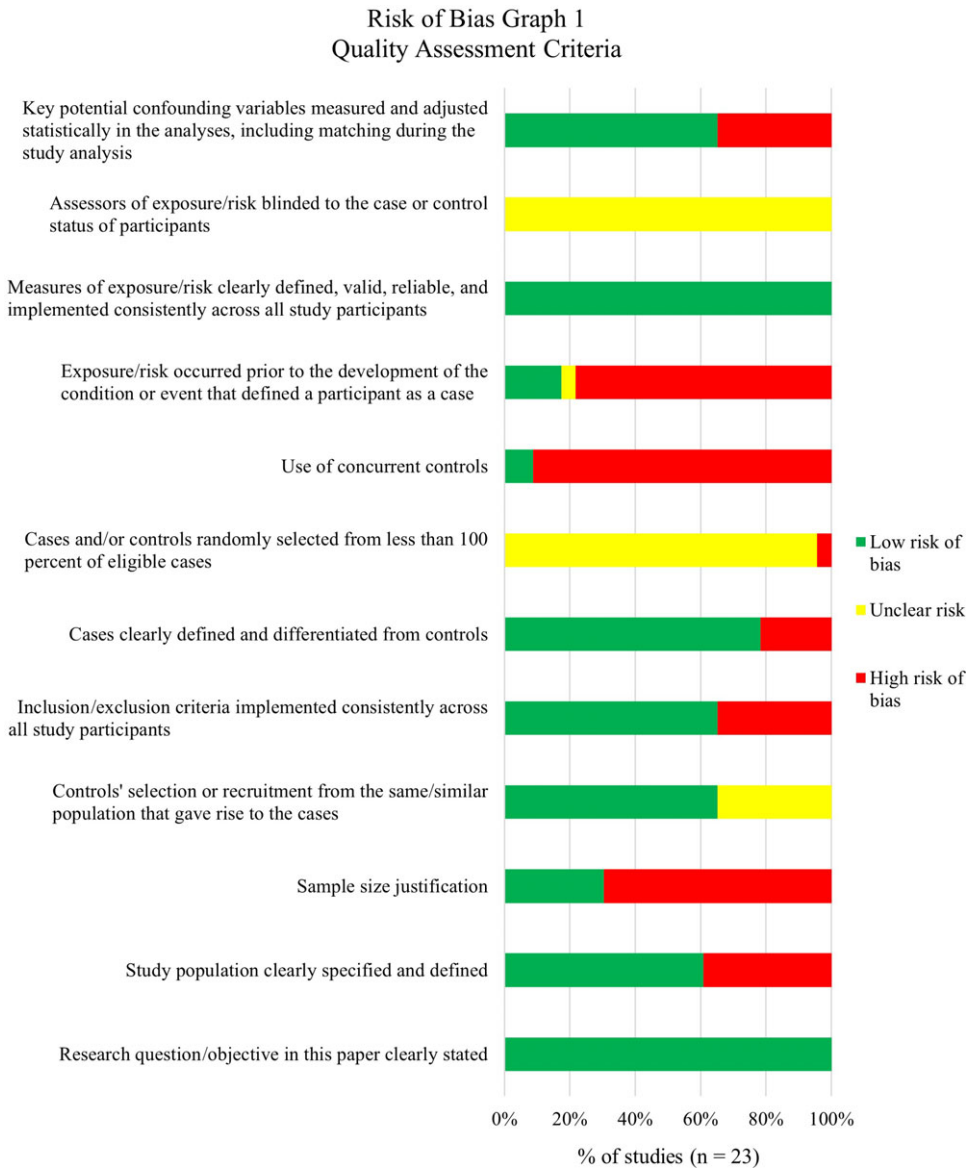

Fig. 2. Risk of bias graph for case–control studies of this review.

classified as 'Good'[22,24,25,27,34,39,45] and four were classified as having a 'Fair' quality[20,29,46,47]. All the eight studies referred to PE; however, four of them also referred to gestational hypertension/PIH[25,29,45,46].

Details of the studies reporting a lack of association between Se and HDP can be found in Tables 3 and 4. Importantly, Da Silva *et al.*[45] observed that maternal serum Se levels did not differ significantly between PE, normotensive or hypertensive (chronic or gestational) pregnant women. Similarly, Rezende *et al.*[46] compared plasma levels of Se among non-pregnant, healthy pregnant, gestational hypertensive and PE women. Se levels were equivalent among pregnant groups (all $P > 0{\cdot}05$). However, non-pregnant women had considerably higher Se levels compared with other groups. On the other hand, despite Elongi *et al.*[39] reported significantly higher urinary Se concentrations in PE women when compared with normotensive women ($P < 0{\cdot}001$), the differences were less marked and statistical significance was lost after adjustment for urine dilution.

Regarding supplemental Se and Se intake, Holmquist *et al.*[25] did not find significant associations between dietary or supplemental Se intake and gestational hypertension, mild-PE or severe PE. Also, McAlpine *et al.*[29] aimed to investigate the effects of supplements on micronutrient status and birth outcomes. Dietary data were self-reported by participants using a FFQ. Supplement use had no significant influence on the incidence of hypertensive disorders ($P > 0{\cdot}05$). Despite this, no detailed data about the type of supplement, duration of supplementation and dose taken by supplemented women were described by the authors.

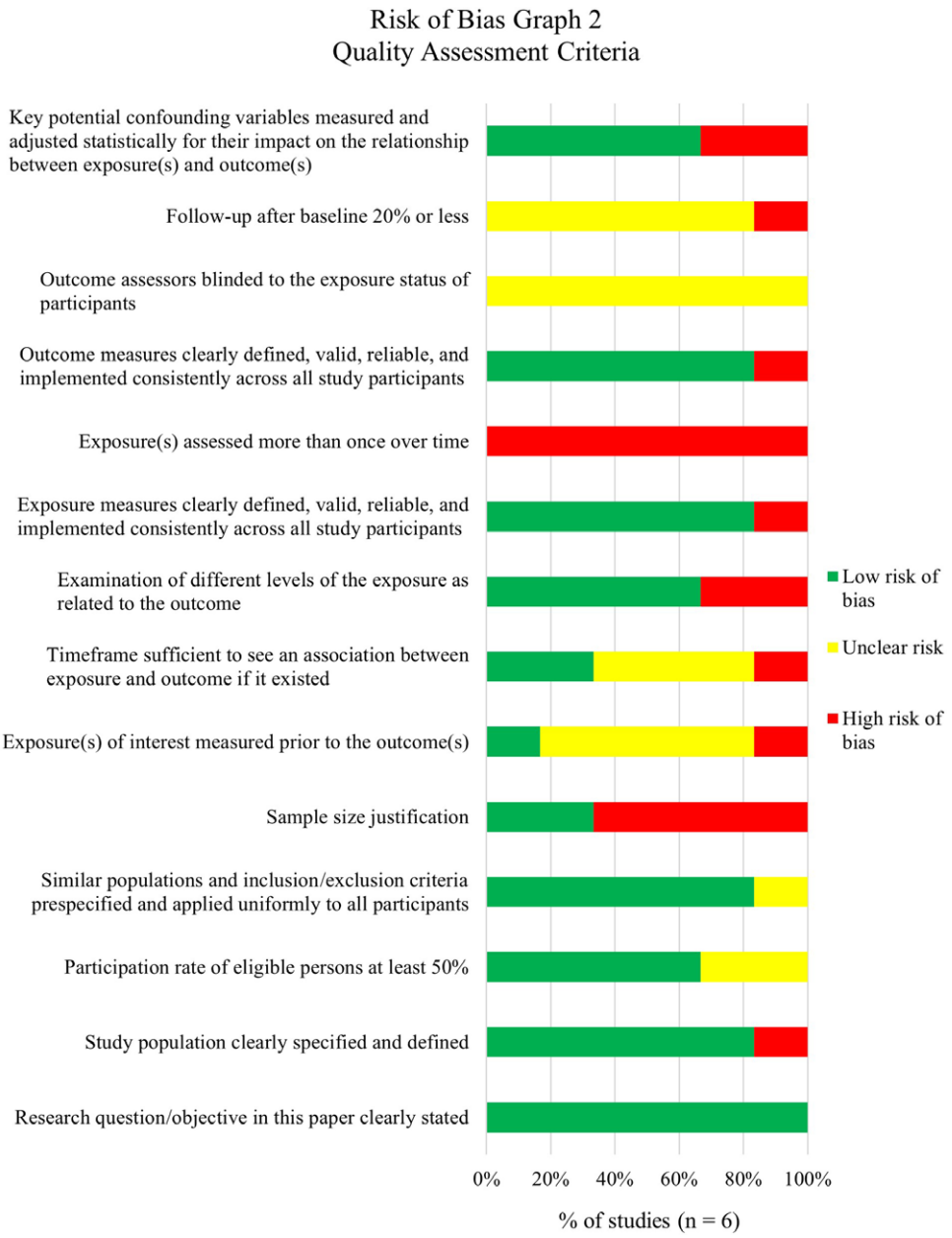

Fig. 3. Risk of bias graph for observational cohort and cross-sectional studies of this review.

Discussion

This systematic review aimed to evaluate and sum up the available evidence of the last decade about the association between Se levels and HDP. Among the thirty included studies, a majority of them, 61 % (*n* 19) of the 'good' or 'fair' studies, reported a negative association between Se and HDP, that is, lower Se levels were associated with the occurrence of HDP or with an increased risk of developing HDP. On the order hand, some studies, 39 % (*n* 11) of the 'good' or 'fair' studies, reported a lack of association.

Women with HDP, present a dysfunctional maternal endothelium, with increased production of reactive oxygen species, and an excessive systemic inflammation[49]. This can explain an increment in Se demand and thus the lower Se levels in women with HDP when compared with normotensive controls, as observed in the majority of studies of this review. In fact, some authors suggest that concentrations of Se decrease proportionally with the severity of previously mentioned phenomena[50].

Low Se availability may thus be a consequence of HDP but, on the other hand, it can be seen as a cause of those conditions. Specifically, Se deprivation may impair correct function of antioxidant Se-dependent enzymes – glutathione peroxidases and thioredoxin reductases – compromising antioxidant defence pathways, which could lead to endothelial dysfunction observed in the pathophysiology of HDP[49,51]. Additionally, Se deficiency could contribute to HDP by disturbing thyroid function and

Table 3. Characteristics of case–control studies included in this review

Authors, publication year	Study type	Country	Study population	Participants	Biological sample	Timepoint and Se quantification method	Main results	Overall study quality
Mazloomi *et al.*, 2021[35]	Case–control	Iran	Pregnant women from Fatemieh Hospital	30 PE women 30 NT pregnant women	Maternal serum	Third trimester AAS	Se concentrations were markedly lower in PE women compared with the NT women (80·15 ± 23·16 ng/l *v.* 110·18 ± 46·70 ng/l, $P < 0·05$)	Fair
McKeating *et al.*, 2021[21]	Nested case–control	Australia	Pregnant women from the Fetal Longitudinal Assessment of Growth study from 2015 to 2016	38 PE woman 193 NT pregnant women	Maternal plasma	Third trimester ICP-MS	Women who later developed PE exhibited decreased concentrations of Se compared with the NT women (57·992 μg/l *v.* 61·390 μg/l) ($P > 0·05$)	Good
Dahabiyeh *et al.*, 2020[37]	Case–control	England, UK	Pregnant and non-pregnant women from Nottingham University Hospitals	17 PE women 17 NT pregnant women 10 healthy non-pregnant women of reproductive age	Maternal serum	Before onset of labour Graphite furnace AAS	Se concentrations were lower in PE women compared with NT pregnant women and healthy non-pregnant women (median (IQR): 40·4 (29·8, 48·6), 62·9 (49·0, 68·2) and 69·5 (61·2, 73·6) μg/l, respectively) ($P < 0·05$)	Fair
Enebe *et al.*, 2020[40]	Case–control	Nigeria	Women attending the antenatal and booking clinics of the University of Nigeria Teaching Hospital	81 PE women 81 NT pregnant women	Maternal serum	Unclear AAS	Se levels were significantly lower in the PE pregnant group when compared with the healthy pregnant controls (0·842 ± 0·71 mg/l *v.* 1·758 ± 3·35 mg/l, $P < 0·05$) The serum levels of Se did not vary significantly by category of PE (with or without severity findings)	Good
Eze *et al.*, 2020[41]	Case–control	Nigeria	Pregnant women from Maternity Unit of the Department of Obstetrics and Gynaecology of the Federal Medical Centre, Owerri, Imo State From November 2014 to November 2016	58 PE women 58 NT pregnant women	Maternal serum	Third trimester Flame AAS	The mean Se level in the PE group (0·67 ± 0·27 μmol/l) was lower than that of the normotensive control (1·20 ± 0·46 μmol/l, $P < 0·05$). This deficiency worsened with the increasing severity of the disease ($P < 0·001$).	Good
Lewandowska *et al.*, 2020[38]	Case–control	Poland	Women from Polish prospective cohort, recruited in 2015–2016	120 PIH women (PE or GH) 443 NT pregnant women	Maternal serum	First trimester ICP-MS	Women developing PIH had significantly lower Se levels compared with the normotensive women (57·56 *v.* 61·62 μg/l, $P < 0·05$).	Good
Bommarito *et al.*, 2019[18]	Nested case–control	USA	Pregnant women from LIFECODES birth cohort From 2006 to 2008	28 PE women 355 NT pregnant women	Maternal urine	Third trimester ICP-MS	Median (IQR) Se levels for PE women were 36·3 (31·2, 46·0) compared with non-PE women 37·0 (29·6, 45·6) An IQR increase in urinary Se was associated with reduced risk of PE (HR: 0·28, 95 % CI (0·08, 0·94)) ($P < 0·05$)	Good
Cinemre *et al.*, 2019[47]	Case–control	Turkey	Pregnant women presenting to a university hospital (unclear) From July 2014 to December 2016	98 PE women 100 NT pregnant women	Maternal plasma	Unclear Graphite furnace AAS	The mean maternal Se levels were higher in pregnant women with PE compared with women without PE (92·56 ± 6·10 μg/l *v.* 86·26 ± 6·33 μg/l, respectively ($P > 0·05$)	Fair
Soobramoney *et al.*, 2019[44]	Case–control	South Africa	Pregnant women from the antenatal clinic of a regional hospital in Durban	33 PE women 33 NT pregnant women	Maternal nail (both finger and toe-nail clippings)	Third trimester ICP-MS	Se levels were similar between PE group and NT group (10 ± 1 μg/g *v.* 10 ± 2 μg/g, $P > 0·05$). However, lower Se levels were significantly related to the severity of PE ($P < 0·05$)	Fair

Table 3. (*Continued*)

Authors, publication year	Study type	Country	Study population	Participants	Biological sample	Timepoint and Se quantification method	Main results	Overall study quality
Al-Hilli *et al.*, 2017[31]	Case–control	Iraq	Women recruited from Babylon Teaching Hospital for Gynecology & Pediatrics	60 PE women 60 NT pregnant women	Maternal serum	Third trimester Graphite furnace AAS	Se levels were significantly lower in patients with PE compared with control group (2·546 ± 0·068 μg/dl *v.* 4·306 ± 0·050 μg/dl), $P < 0·05$)	Fair
Da Silva *et al.*, 2017[45]	Case–control	Brazil	Pregnant women from antenatal or obstetric admissions of Hospital de Clínicas de Porto Alegre From December 2014 to October 2015	20 hypertensive (chronic and gestational hypertension) 38 PE women 32 NT pregnant women	Maternal serum	Third trimester ICP-MS	Se levels were not significantly different between groups, with an average of 56·4 ± 15·3 μg/l in the control group, 53·2 ± 15·2 μg/l in the hypertension group and 53·3 ± 16·8 μg/l in the pre-PE group ($P > 0·05$). When comparing only PE women with controls, the difference was still not significant. Among patients with PE, 52·6 % had the severe form. Serum Se levels in these patients also did not differ significantly from those of controls ($P = 0·77$)	Good
Maduray *et al.*, 2017[42]	Case–control	South Africa	Pregnant women from a large urban regional hospital	43 PE women 23 NT pregnant women	Maternal hair (from pubic area) and serum	At delivery ICP-MS	Although median hair Se was higher in the PE group compared with the NT group (24·42 ± 1·78 μg/g *v.* 23·93 ± 2·62 μg/g), this was not significantly different Serum Se levels were significantly lower in the PE group compared with the NT group (0·06 ± 0·01 mg/l *v.* 0·14 ± 0·01 mg/l, $P < 0·05$)	Poor
Nnodim *et al.*, 2017[43]	Case–control	Nigeria	Pregnant women attending General Hospital Owerri From February 2014 to April 2015	100 PE women 100 NT pregnant women	Maternal serum	Third trimester AAS	Se levels were significantly decreased in PE group when compared with NT group (63·21 ± 4·87 μg/l *v.* 69·18 ± 2·44 μg/l, $P < 0·05$)	Fair
Elongi *et al.*, 2016[39]	Case–control	DR Congo	Women from the Obstetric ward and Intensive Care Unit of General Hospital of Kinshasa From March to September 2011	88 PE women 88 NT pregnant women	Maternal 24-h urine collections	Third trimester ICP-MS	Se levels were significantly higher in PE women when compared with NT women (44·6 μg/l *v.* 27·2 μg/l, $P < 0·05$). However, the daily urinary excretion of Se was not significantly different between the groups (38·8 μg/d PE *v.* 31·0 μg/d NT, $P > 0·05$)	Good
Haque *et al.*, 2016[33]	Case–control	Bangladesh	Pregnant women from Noakhali Medical College Hospital From June 2013 to January 2014	74 PE women (52 mild and 22 severe PE) 118 NT pregnant women	Maternal serum	PE group: third trimester NT group: second trimester Flame AAS	Se levels were significantly lower in PE pregnant women (23·76 ± 0·64 μg/l *v.* NT women 32·18 ± 1·22 μg/l) ($P < 0·05$) A statistically significant difference ($P < 0·05$) was found between serum Se concentrations for mild and severe PE women	Fair
Laine *et al.*, 2015[20]	Nested case–control	USA	Pregnant women from MOTOR cohort study From December 2003 to October 2007	86 PE women 86 NT pregnant women	Placenta (from central zone)	At delivery ICP-MS	Placental Se levels were lower in PE group (237·5 ng/g) when compared with NT women (254·5 ng/g), but the difference was not statistically significant The authors reported an OR of 1·0 (95 % CI (0·99, 1·0)) for PE in relationship to placental Se	Fair

Table 3. (*Continued*)

Authors, publication year	Study type	Country	Study population	Participants	Biological sample	Timepoint and Se quantification method	Main results	Overall study quality
Mistry *et al.*, 2015[22]	Nested case–control	Australia, New Zealand, UK	Pregnant women from SCOPE study From November 2004 to February 2011	244 PE women 472 NT pregnant women	Maternal plasma	Second trimester ICP-MS	Se levels were similar among PE and NT women in pre-disease samples (median, IQR) was 79·0 (71·8, 87·4) μg/l in cases and 79·6 (73·1, 86·8) μg/l in controls). No association between Se levels and HDP were found	Good
Rezende *et al.*, 2015[46]	Case–control	Brazil	Pregnant women from Maternity of Ribeirao Preto	184 pregnant women (61 diagnosed with gestational hypertension, 37 with PE and 51 healthy pregnant women) 35 non-pregnant women	Maternal plasma	Third trimester ICP-MS	Se levels were similar among pregnant groups (healthy pregnant, gestational hypertension women and PE; all $P > 0·05$)	Fair
Ghaemi *et al.*, 2013[19]	Nested case–control	Iran	Pregnant women from Obstetric clinics of Shiraz University of Medical Sciences From June to March 2011	38 PE women 38 NT pregnant women	Maternal plasma	Second and third trimesters AAS	Se levels in PE women were significantly lower than those in controls at second trimester (70·63 ± 21·41 *v.* 82·03 ± 15·54 μg/l,) and at third trimester (71·22 ± 16·95 *v.* 80·27 ± 17·12 μg/l) ($P < 0·05$) Se concentrations lower than 62·2 μg/l were associated with a higher risk of PE	Good
Farzin and Sajadi, 2012[32]	Case–control	Iran	Pregnant women from Women's clinics of Tehran University and Sarem Hospital	60 PE women 60 NT pregnant women	Maternal serum	Third trimester Graphite furnace AAS	Se levels were significantly lower in PE group (8·82 ± 2·10 μg/dl) compared with the NT group (10·47 ± 2·78 μg/dl) ($P < 0·05$)	Fair
Katz *et al.*, 2012[23]	Prospective case–control	Israel	Pregnant women from Soroka University Medical Center	43 severe PE women and their newborn 80 NT pregnant women and their newborn	Maternal plasma and cord blood	Plasma: third trimester Cord blood: before delivery of the placenta ICP-MS	Se levels were significantly lower in maternal and fetal arterial and venous cord blood of the PE group ((98·6 ± 24·2; 82 ± 17·8; 82·1 ± 17·4 μg/l) *v.* (110·7 ± 19·4; 111·6 ± 17·6; 107·1 ± 25·7 μg/l)) ($P < 0·001$)	Fair
Kim *et al.*, 2012[34]	Case–control	South Korea	Pregnant women admitted for delivery at Mokdong Hospital, Ewha Womans University, Seoul From 2008 to 2007	30 PE women 29 NT pregnant women	Serum	At delivery INAA	Se levels were not different between groups	Good
Negi *et al.*, 2012[36]	Case–control	India	Pregnant women from University Hospital, Banaras Hindu University	19 PE women 14 E women 18 NT pregnant women	Cord blood	At delivery Unclear	Se concentrations were significantly reduced in PE women (18·58 ± 5·21 μg/l) and E women (16·34 ± 5·23 μg/l) in comparison with that of control group (22·17 ± 4·19 μg/l) ($P < 0·005$)	Fair

AAS, atomic absorption spectrometry; E, eclampsia; GH, gestational hypertension; ICP-MS, inductively coupled plasma – mass spectrometry; IQR, interquartile range; INAA, instrumental neutron activation analysis; PE, pre-eclampsia; PIH, pregnancy-induced hypertension; NT, normotensive.

Table 4. Characteristics of non-case–control studies included in this review

Authors, publication year	Study type	Country	Study population	Participants	Biological sample	Timepoint and Se quantification method	Main results	Overall study quality
Holmquist *et al.*, 2021[25]	Prospective cohort	Norway	Pregnant women from the Norwegian Mother, Father and Child Cohort Study From 1999 to 2008	69 972 women for analysis of Se intake through FFQ 2572 women for analysis of Se status	Maternal whole blood	Second trimester ICP-MS	The main outcome was pregnancy-induced hypertensive disorders, with sub-analyses for PIH and PE Participants had a median dietary Se intake of 53 μg/d (IQR 44–62). Dietary Se intake (adjusted (a) OR 1·03) and Se blood status (aOR 1·03) were not significantly associated with PIH or PIH subgroups (gestational hypertension and PE)	Good
Ambad *et al.*, 2020[28]	Cross-sectional	India	Pregnant women from Shalinitai Meghe Hospital	150 PE pregnant women: 100 without supplementation (group I) 50 with supplementation (group II) 100 NT pregnant women (group III)	Maternal serum	Unclear Unclear	Se levels were significantly lower in PE women without supplementation when compared with NT women (58·23 ± 8·44 *v.* 62·33 ± 9·42, $P < 0·01$) In supplementation and without supplementation groups, no significant differences were seen in levels of Se Se levels were lower in supplemented women compared with NT women (60·48 ± 7·63 *v.* 62·33 ± 9·42, $P > 0·05$)	Poor
Lewandowska *et al.*, 2019[26]	Prospective cohort	Poland	Women from the Wielkopolska region (recruited from 2015 to 2016)	121 PIH women (PE or GH) 363 NT pregnant women	Maternal serum	First trimester ICP-MS	The mean serum Se level was significantly lower in the PIH group compared with control (57·51 *v.* 62·89 μg/l, $P < 0·05$)	Good
Liu *et al.*, 2019[27]	Retrospective cohort	USA	Women from the Boston Birth Cohort	115 PE women 1159 NT pregnant women	Maternal whole blood (erythrocytes)	After delivery (within 24–72 h) ICP-MS	The mean levels of Se were similar between the groups (274·0 μg/l *v.* 276·0 μg/l, $P > 0·05$)	Good
McAlpine *et al.*, 2019[29]	Cross-sectional cohort	Australia	Pregnant women from Gold Coast University Hospital or the Royal Brisbane and Women's Hospitals From 2017 to 2018	80 pregnant women using a multivitamin supplement with Se 42 pregnant women without Se supplement Assessment of Se intake through FFQ	Maternal serum	Third trimester ICP-MS	Women using Se supplement were found to exhibit mean dietary values higher than the recommended daily intake (122 μg/d *v.* 79 μg/d, $P < 0·05$) However, these excesses did not translate to serum values, as no significant differences were found between elemental means in supplement and non-supplement users. Supplement use had no significant influence on the incidence of hypertensive disorders ($P > 0·05$)	Fair
Choi *et al.*, 2016[24]	Prospective cohort	South Korea	Pregnant women from Samsung Medical Center From 2012 to 2013	245 pregnant women 527 healthy adults (300 men and 227 non-pregnant women)	Maternal serum	First, second and third trimesters ICP-MS	Se concentrations were lower in pregnant women than in the healthy non-pregnant women (94·0 *v.* 140·0 μg/l, $P < 0·01$). Furthermore, concentrations of Se varied significantly during the three trimesters ($P < 0·05$) (average values of Se decreasing over the trimesters) Among the 245 pregnant women, 5 (2·0 %) experienced PE; no significant associations were observed between low Se and PE	Good

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Table 4. (*Continued*)

Authors, publication year	Study type	Country	Study population	Participants	Biological sample	Timepoint and Se quantification method	Main results	Overall study quality
Rayman *et al.*, 2015[30] (subtype of Rayman *et al.*, 2014)[48]	Randomised controlled trial 230 primiparas randomised to Se supplementation with 60 µg/d (Se-enriched yeast) or placebo, from 12 to 14 weeks of gestation until delivery	United Kingdom	Pregnant women from SPRINT study	20 HDP women (gestational hypertension or PE) 207 NT pregnant women	Maternal whole blood and toenail	Whole blood at second and third trimesters Toenail at second trimester ICP-MS (whole blood) and INAA (toenail)	The median toenail Se concentration in women who developed HDP was significantly lower than that in other women (0·57 µg/g *v.* 0·61 µg/g, $P < 0·05$) No Se levels in whole blood were available in the results In Se-treated group, a significant increase was observed in whole-blood Se concentration from 12 to 35 weeks After exclusion of non-compliers with Se treatment, Se supplementation was found to significantly reduce the OR for PE/PIH (OR 0·30, 95 % CI (0·09, 1·00), $P = 0·049$)	Good

AAS, atomic absorption spectrometry; E, eclampsia; FFQ, food frequency questionnaire; GH, gestational hypertension; ICP-MS, inductively coupled plasma – mass spectrometry; INAA, instrumental neutron activation analysis; IQR, interquartile range; PE, pre-eclampsia; PIH, pregnancy-induced hypertension; NT, normotensive.

increasing TSH production[52] which has been suggested as a risk factor for gestational hypertension[53].

Three studies of this review[24,26,38] measured Se levels in the first trimester of pregnancy, that is, before the diagnosis of HDP (after 20 weeks) took place, and two of them[26,38] ('good' studies) found a negative association between Se and HDP. Lewandowska *et al.*[26] additionally found that the risk of developing HDP increased along with decreasing levels of Se in the first trimester. These findings suggest that adequate Se levels from an early stage of pregnancy, or even in the preconceptional period, have an important and protective role against HDP. On the other hand, our revision included six studies that evaluated Se levels in blood/serum or in placenta at delivery or hours after delivery. Of these, the majority revealed a negative association between Se levels and PE, which corroborates that Se deficiency could also be seen as a consequence of HDP.

Like the included study of Rayman *et al.*[30], some studies from literature combine the outcomes of PE and gestational hypertension/PIH in their analysis since the distinction between the two is not always completely obvious and consensual[54,55]. PE was the most reported HDP in the included studies of this review. To date, few other reviews have been carried out about this theme. For example, a negative association between Se and PE was also reported in the year 2016 by Xu *et al.*[17]. The researchers included in their meta-analysis thirteen observational studies and three RCT (in two of them Se supplementation began in the first trimester with a duration of 5–6 months, while the other one began on late pregnancy with a duration of 6–8 weeks). In the meta-analyses, they observed lower Se blood levels in women with PE, when compared with normotensive controls, and also concluded that Se supplementation in pregnant women was associated with a lower risk of developing PE (the relative risk for PE was 0·28). On the other hand, Rumbold *et al.*[56] conducted a systematic review with meta-analysis about antioxidants for preventing PE, but only one study about Se was included – Han *et al.*[57] – in which fifty-two women were supplemented with 100 µg/d of Se for 6–8 weeks during late pregnancy, but no differences between the Se-treated and the control groups in preventing PE were found. This study was also the only included study referring to Se in the systematic review conducted by Salles *et al.*[58].

Our review shows strong evidence in favour of a negative association between Se and HDP. Nevertheless, some of the included studies were not in agreement with this. The disparity among some available evidence could be due to different study types of the included studies, to differences in sample size or in characteristics of the study population, as well as due to the heterogeneity in biological samples used, gestational age of sample collection and Se quantification method. In fact, the proportion of case–control studies was higher in the group reporting a negative association (84 % case–control) when compared with the proportion of case–control studies in the group that did not find associations (64 % case–control). Also, the mean sample size of studies finding a negative association was smaller (mean *n* 179) when compared with the mean sample size of studies that did not find significant associations (mean *n* 551). Regarding timepoint of quantification, the proportion of studies quantifying Se during pregnancy

(before delivery) was higher in the group reporting a negative association (74 %, *n* 14) when compared with the group that did not find associations (64 %, *n* 7). Finally, the proportion of studies using inductively coupled plasma – MS to measure Se was lower in the group reporting a negative association (36 %, *n* 7) when compared with the group that did not find associations (81 %, *n* 9).

Despite this heterogeneity among studies, the proportion of studies using blood (plasma/serum/whole blood) samples was similar in the group that found negative associations (84 %, *n* 16) when compared with the group that did not report associations (81 %, *n* 9).

Still regarding biological samples used, most of the included studies used maternal serum, plasma, or whole blood for Se quantification. Plasma/serum and erythrocyte are the samples most commonly used for measurement of Se levels, and they reflect short-term and long-term Se status, respectively[59]. On the other hand, blood Se concentration is generally considered a useful measure of both Se status. Some authors consider erythrocytes as the more precise and stable biomarker for quantification of Se concentration[58,60,61,62]; however, only one study of this review[27] measured concentrations of Se in erythrocytes. Urine is also commonly used because of the convenience and low discomfort associated with the collection. Two of the included studies used maternal urine, but only in one of them Se concentrations in urine were adjusted for dilution and converted to daily amounts. In fact, daily urinary excretion of Se is closely associated with plasma Se concentrations[59]. In general, we considered that a great majority of the included studies used adequate biological samples for Se quantification.

Additionally, this review included three studies of 'good' quality suggesting that an increase in Se levels is protective against HDP (of these, only one was an RCT of Se supplementation), but two other studies of 'good' or 'fair' quality did not find evidence supporting that Se supplementation reduces the risk of HDP. So, the gathered evidence in favour of Se supplementation to prevent HDP is not sufficient.

In fact, despite the benefits of Se as a protector against oxidative damage are well known, Se supplementation is not yet preconised in guidelines for prevention and/or management of HDP, because there is a lack of knowledge about the complex interactions between Se and other different micronutrients, as well as about individual response to different doses of Se[63]. Currently, for example, when Ca intake is likely to be low (<600 mg/d) in cases of pregnant women with risk factors for PE, the ISSHP recommends supplementation with Ca (1·2–2·5 g/d) in addition to aspirin. In this context, would Se supplementation interfere in any way with the already preconised Ca supplementation? Considering the relevance of Se for thyroid function, would Se supplementation be compatible with the already preconised iodine supplementation?

Our study has important strengths and some limitations. Strengths of our review include the use of a search methodology in line with the current recommendations for systematic reviews, with a comprehensive and sensitive search strategy, employing multiple databases, searching for grey literature, paired selection, data extraction by multiple reviewers and the use of quality assessment tools. The use of a standardised tool such as the NHLBI Study Quality Assessment Tools allowed a better and systematised characterisation of each article. Also, all the studies retrieved in our search were written in English, and for that reason, no studies were excluded by language. Another strength is that our revision did not exclude studies based on the type of biological sample, on the type of HDP and, importantly, on the timepoint for Se quantification which enabled us to suggest about a putative role of Se deficiency in the pathogenesis but also as a consequence of HDP. Due to huge variations and heterogeneity of the included articles, a quantitative meta-analysis was not performed.

In contrast, this review has potential limitations: the exclusion of articles based on publication date could have excluded some relevant studies. Nevertheless, the last available systematic review about this theme was published in 2016 and it included papers until 2014, which ensures an overlap of 4 years with our search. Another limitation is that our search retrieved only one RCT while the majority of the included studies were observational case–controls, which do not allow to draw conclusions about causality.

Conclusion

In conclusion, this review provides an important amount of quality evidence suggesting that low Se levels associate with the occurrence of HDP, corroborating the most recent meta-analyses about this topic[17]. In addition, this review emphasises that low Se could be a player in the pathogenesis of HDP, but it could also be a consequence of those diseases. Nevertheless, the gathered information is not enough to underlie a recommendation for Se supplementation in pregnancy to protect against HDP.

In fact, several questions remain unanswered and require urgent attention from the scientific community: (a) what would be the best time to begin Se supplementation during or before pregnancy; (b) what would be the adequate daily dose of Se for an effective protection against HDP; (c) what would be the adequate duration of supplementation; (d) who would be the target population: all pregnant women or only women at high risk for HDP; (e) what would be the health risks for the mother and the child and (f) what micronutrient interactions should be considered.

Despite a recent increase and investment in the scientific research about this theme (studies published in the last 3 years account for 47 % (*n* 14) of the included studies), this review emphasises the need for further well-designed, large and high-quality, double blind, placebo-controlled randomised trials that may find answers to the abovementioned questions and provide blunt evidence regarding the benefits of Se supplementation during pregnancy to prevent HDP.

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None of the authors has any conflict of interest to declare.

Supplementary material

For supplementary material referred to in this article, please visit https://doi.org/10.1017/S0007114522003671

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