Selenium, Zinc, And Copper In Preeclampsia: Research Trends, Direction Of Evidence, And Knowledge Gaps

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Abstract

Selenium (Se), zinc (Zn), and copper (Cu) are involved in antioxidant defence, endothelial regulation, and placental function, but their circulating concentrations in preeclampsia remain inconsistently reported. To characterize publication trends, methodological orientation, direction of observational evidence, and priority research gaps for maternal circulating Se, Zn, and Cu in preeclampsia. Scopus and PubMed were searched through 30 July 2026. After investigator-resolved deduplication in Rayyan, 280 unique records formed the bibliometric corpus. Protocol 1 included observational human studies in pregnant women, with preeclampsia as the primary outcome, measuring Se, Zn, or Cu in maternal serum, plasma, leukocytes, or erythrocytes. Evidence mapping was restricted to 2006-2025. Human observational studies dominated the corpus (216/280; 77.1%), followed by experimental/basic science studies (21; 7.5%), systematic reviews/meta-analyses (14; 5.0%), narrative reviews (11; 3.9%), intervention studies (11; 3.9%), and other formats (7; 2.5%). Forty-eight reports met Protocol 1; 33 were eligible within the 20-year window and 32 full texts, representing 30 unique populations, were included. Only five populations used prospective or prediagnostic sampling. Selenium showed the most consistent inverse pattern. Zinc was generally lower but heterogeneous, whereas copper findings were bidirectional; the Cu/Zn ratio was consistently higher in three studies. The field is association-rich but temporality-poor. Priorities are serial early-pregnancy cohorts, preeclampsia-phenotype stratification, adjustment for nutritional and inflammatory factors, matrix-specific analytical standardization, and external validation before biomarker-guided interventions.

Keywords: selenium; zinc; copper; preeclampsia; bibliometric analysis; evidence mapping; oxidative stress

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INTRODUCTION

Preeclampsia is a pregnancy-specific multisystem disorder characterized by new-onset hypertension after 20 weeks of gestation, accompanied by proteinuria and/or maternal organ or uteroplacental dysfunction. It remains a major contributor to maternal and perinatal morbidity worldwide. Contemporary concepts describe preeclampsia as a heterogeneous syndrome arising from abnormal placentation, angiogenic imbalance, systemic endothelial dysfunction, inflammation, and oxidative stress rather than a single uniform disease process [1,2].

Trace elements have attracted sustained attention in this context because selenium, zinc, and copper participate in antioxidant enzymes, redox signaling, immune regulation, vascular function, and placental development. Selenium is incorporated into selenoproteins such as glutathione peroxidases and thioredoxin reductases. Zinc contributes to protein synthesis, cellular signaling, membrane stability, and the antioxidant defence system. Copper is required for copper-zinc superoxide dismutase and ceruloplasmin, but circulating copper is also influenced by the acute-phase response. These biological roles make trace-element imbalance plausible in preeclampsia, although they do not establish causality [3].

The empirical literature is difficult to interpret. Studies differ in gestational timing, biological matrix, analytical platform, case definition, nutritional context, disease severity, and adjustment for inflammation. Many investigations obtain samples after clinical diagnosis, so an observed concentration may reflect disease-related redistribution rather than an antecedent exposure. Serum, plasma, whole blood, erythrocytes, leukocytes, placental tissue, urine, and cord blood also represent different biological compartments and should not be treated as interchangeable.

Previous reviews have generally evaluated one element or used conventional meta-analysis. A combined bibliometric analysis and systematic evidence map can distinguish the broader publication landscape from the narrower body of directly relevant observational

evidence. This study therefore aimed to characterize research trends in the 280-record combined corpus and to map primary observational evidence on maternal circulating Se, Zn, and Cu in preeclampsia during the 20 complete calendar years from 2006 through 2025.

METHODS

Study Design and Reporting Framework

This study combined descriptive bibliometric analysis with a nested systematic evidence map. The identification and selection process was reported using the PRISMA 2020 framework [4], the search process followed PRISMA-S principles [5], and the structured narrative synthesis followed SWiM reporting concepts [6]. The review was not registered prospectively. The 2006-2025 restriction was introduced as a protocol amendment before final evidence extraction to represent 20 complete calendar years and avoid incomplete indexing for 2026.

Data Sources and Search Strategy

Scopus and PubMed were searched from database inception through 30 July 2026. Search concepts covered preeclampsia and historical synonyms, selenium, zinc, copper, trace elements or trace minerals, and terms indicating maternal circulating concentrations. The combined 280 unique records formed the descriptive bibliometric corpus. Because cited references, citation counts, affiliations, and author keywords were more complete and standardized in Scopus, detailed performance and network indicators were calculated from the 256-record Scopus subset; the 24 PubMed-only records remained part of the combined descriptive corpus and screening process.

Table 1. Core database search concepts.

Database	Search structure
Scopus	TITLE-ABS-KEY ((selenium OR zinc OR copper OR "trace element*" OR "trace mineral*") AND (preeclamp* OR pre-eclamp* OR "pregnancy toxemia" OR "EPH gestosis") AND (serum OR plasma OR blood OR level* OR concentration* OR status))
PubMed	(Pre-Eclampsia[MeSH] OR preeclamp*[Title/Abstract] OR pre-eclamp*[Title/Abstract]) AND (Selenium[MeSH] OR Zinc[MeSH] OR

	Copper[MeSH] OR Trace Elements[MeSH] OR corresponding free-text terms) AND (serum OR plasma OR blood OR level* OR concentration* OR status)[Title/Abstract]

Record Management and Eligibility

Scopus and PubMed records were imported into Rayyan. Investigator-reviewed duplicate resolution reduced 433 database records to 280 unique records. All 280 records were retained for bibliometric description and were screened against Protocol 1 for the evidence map. The contemporary evidence synthesis was subsequently restricted to publications dated 1 January 2006 through 31 December 2025.

Studies were eligible when they: (1) were observational human studies involving pregnant women; (2) evaluated preeclampsia as the primary outcome, including preeclampsia occurrence, risk, or severity; and (3) directly measured selenium, zinc, or copper in maternal serum, plasma, leukocytes, or erythrocytes. Eligible designs comprised case-control, cross-sectional, cohort, prospective cohort, and nested case-control studies. Studies were excluded when they were non-observational, including randomized or non-randomized interventions, reviews, meta-analyses, protocols, case reports, animal or in-vitro studies; evaluated a pregnancy outcome other than preeclampsia as the primary outcome; did not measure a target element; used only placenta, urine, hair, nails, cord blood, amniotic fluid, or another ineligible matrix; or did not provide a preeclampsia-specific result. Reports using additional compartments were retained only when an eligible maternal circulating matrix was also analyzed.

Bibliometric and Evidence-Map Variables

Bibliometric variables included publication year, journal, authorship, country affiliations, indexed keywords, and Scopus citation counts. Citation-based indicators were calculated only for Scopus-indexed records because PubMed does not provide directly comparable citation data. Metadata were harmonized and analyzed using custom Python routines and spreadsheet verification.

To examine methodological development, all 280 bibliometric records were additionally coded by publication orientation using titles, abstracts, indexed keywords, and database publication-type metadata. Categories were mutually exclusive and applied hierarchically: systematic review/meta-analysis; narrative or scoping review; human intervention study; experimental/basic science study (animal, in-vitro, or cell-based); other analytical or non-primary publication (including protocol, case report, conference abstract, erratum, and Mendelian-randomization analysis); and human observational study. Ambiguous reports were assigned conservatively to the category most clearly supported by the available metadata. Temporal changes were summarized across complete publication periods; records from 2026 were retained in the overall corpus but excluded from period-comparison graphics because the year was incomplete.

For eligible observational studies, extracted variables included publication year, country, observational design, sample size, gestational timing, eligible biological matrix, analytical method, target element, comparison group, and direction of association. A result was categorized as lower/inverse when the target concentration was significantly lower in preeclampsia or a higher concentration was associated with lower risk or severity; higher/positive when the concentration was higher in preeclampsia or positively associated with risk or severity; and no difference when the reported association was non-significant. Companion or secondary publications from the same underlying cohort were retained descriptively but consolidated at the study-population level for direction counting.

Synthesis and Ethical Considerations

Results were summarized using counts and percentages. Meta-analysis was not performed because of heterogeneity in eligible matrices, sampling periods, units, analytical platforms, observational designs, and preeclampsia definitions. The direction-of-evidence synthesis therefore describes consistency rather than pooled magnitude or certainty. No intervention studies were included. A formal risk-of-bias assessment was not used to weight

the evidence map because the primary objective was to characterize distribution, direction, and knowledge gaps.

RESULTS

Study Selection

The searches identified 433 records: 256 from Scopus and 177 from PubMed. Investigator-resolved deduplication in Rayyan removed 153 duplicate records, leaving 280 unique records for bibliometric analysis and screening. Protocol 1 screening retained 48 observational human reports with preeclampsia as the primary outcome and eligible maternal Se, Zn, or Cu measurements. Fifteen reports were published before 2006 and were removed from the 20-year evidence window. Thirty-three reports were sought for retrieval; one eligible 2013 report could not be obtained. Thirty-two full-text observational reports were included in the systematic evidence map. After consolidating two sets of companion publications arising from previously reported cohorts, direction-of-evidence counting represented 30 unique study populations (Figure 1).

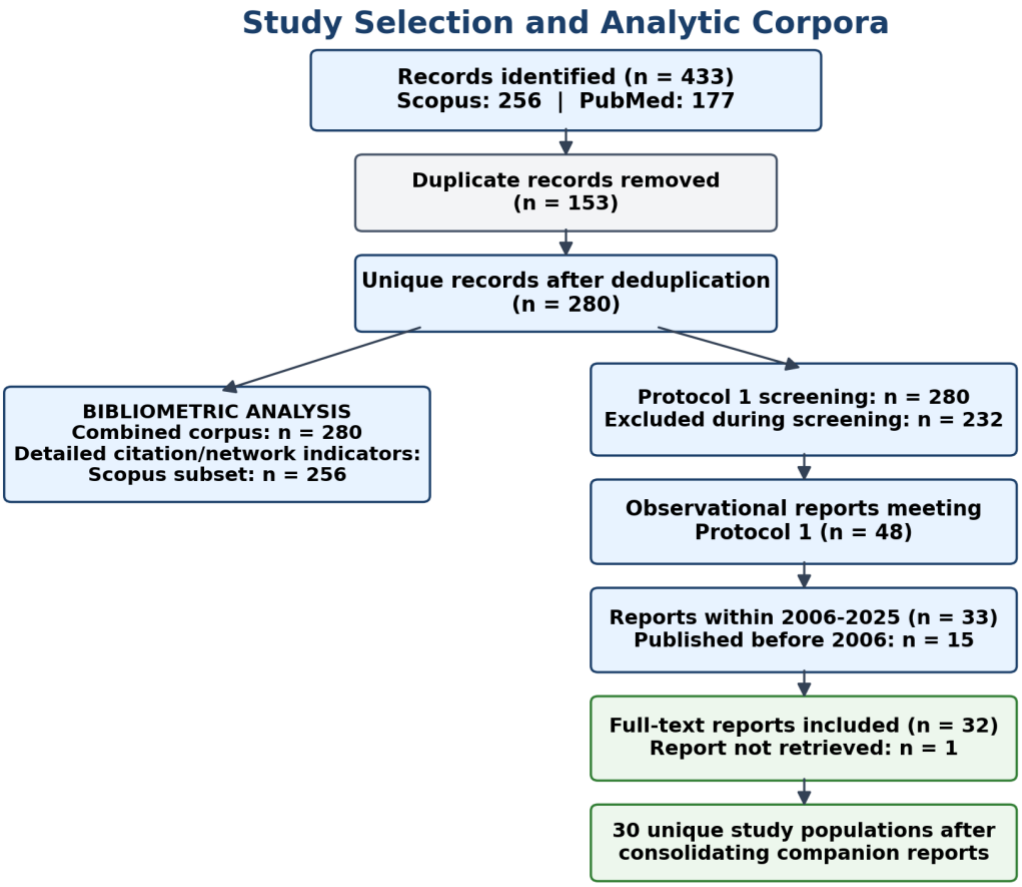

Figure 1. PRISMA-style flow showing the 280-record bibliometric corpus and selection of 32 observational reports for the 2006-2025 evidence map.

Bibliometric Landscape

The combined bibliometric corpus contained 280 unique records. Detailed performance indicators were derived from the 256 Scopus-indexed records, which spanned 1949-2026, 164 sources, 1,291 unique authors, and affiliations from 47 countries. Publication activity was limited before 2000 and increased substantially after 2010. In the Scopus subset, 129 publications (50.4%) appeared from 2015 onward, and the highest annual output occurred in 2015 and 2021, with 14 publications in each year (Figure 2).

The leading Scopus-indexed source was Biological Trace Element Research (n = 16), followed by Journal of Trace Elements in Medicine and Biology (n = 10) and Nutrients (n = 7). Affiliation parsing identified the United States (n = 34), China (n = 24), the United Kingdom (n = 20), Iran (n = 19), and Germany and Turkey (n = 17 each) as the largest contributors;

internationally co-authored records were counted for each represented country. Indonesia contributed ten Scopus-indexed publications. At export on 29 July 2026, the Scopus subset had 7,172 citations and an h-index of 43. Frequent indexed themes included pregnancy, preeclampsia, zinc, copper, selenium, blood, placenta, oxidative stress, and antioxidant enzymes.

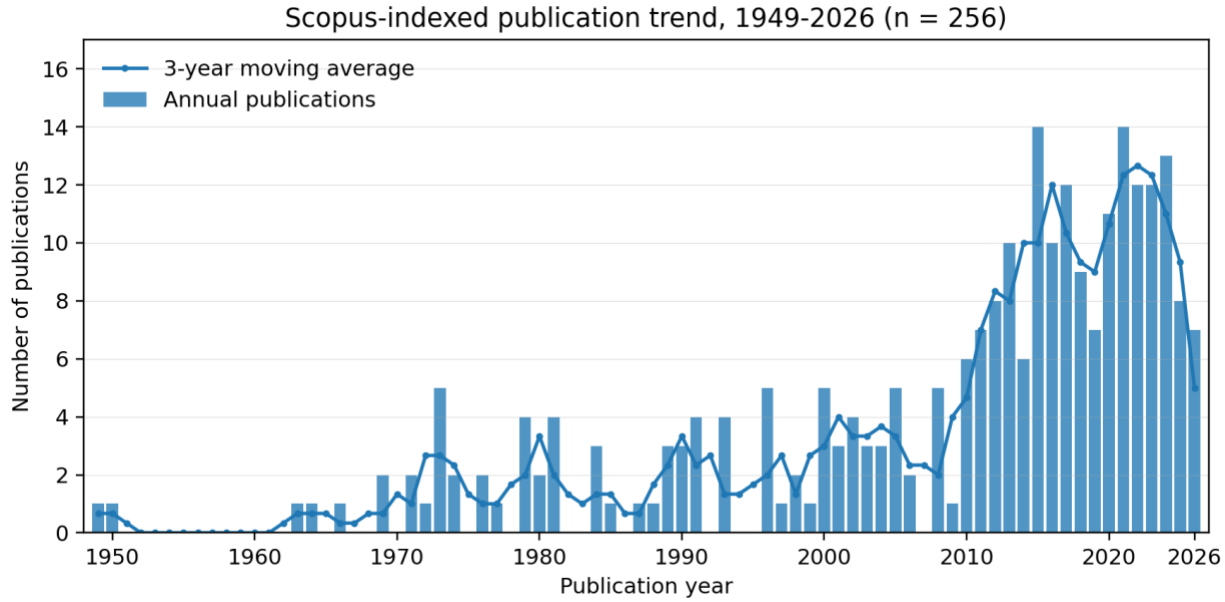

Figure 2. Annual Scopus-indexed publication output on selenium, zinc, copper, trace elements, and preeclampsia, 1949-2026.

Table 2. Summary of the bibliometric corpus, publication orientation, and observational evidence map.

Domain	Indicator	Value
Bibliometric corpus	Unique records after Rayyan deduplication	280
Database composition	Scopus records / PubMed-only records	256 / 24
Scopus analytic subset	Publication years	1949-2026
Scopus analytic subset	Journals/sources	164
Scopus analytic subset	Unique authors	1,291
Scopus analytic subset	Countries represented	47
Publication growth	Published from 2015 onward	129 (50.4%)
Publication growth	Peak years	2015 and 2021 (n = 14 each)
Scopus analytic subset	Citations / h-index	7,172 / 43

Domain	Indicator	Value
Publication orientation	Human observational studies	216 (77.1%)
Publication orientation	Experimental/basic science studies	21 (7.5%)
Publication orientation	Systematic reviews/meta-analyses	14 (5.0%)
Publication orientation	Narrative/scoping reviews	11 (3.9%)
Publication orientation	Human intervention studies	11 (3.9%)
Publication orientation	Other analytical/non-primary publications	7 (2.5%)
Evidence map	Full-text reports / unique populations	32 / 30
Evidence map	Eligible matrices	Serum, plasma, leukocytes, erythrocytes
Evidence map	Prediagnosis/prospective sampling	5 study populations

Evolution of Publication Types and Study Designs

Classification of all 280 records showed that human observational research accounted for 216 publications (77.1%). Experimental or basic-science studies contributed 21 records (7.5%), systematic reviews and meta-analyses 14 (5.0%), narrative or scoping reviews 11 (3.9%), human intervention studies 11 (3.9%), and other analytical or non-primary formats 7 (2.5%). The corpus therefore remained strongly oriented toward observational association rather than intervention or causal evaluation. Methodological diversification became more visible after 2015. Systematic reviews and meta-analyses first appeared in 2015 and increased to five publications in 2016-2020 and eight in 2021-2025. Nevertheless, observational studies still represented 44 of 66 publications (66.7%) in 2021-2025, compared with only three intervention studies (4.5%). Experimental/basic-science and evidence-synthesis publications each accounted for eight records (12.1%) in the most recent complete five-year period (Figure 3).

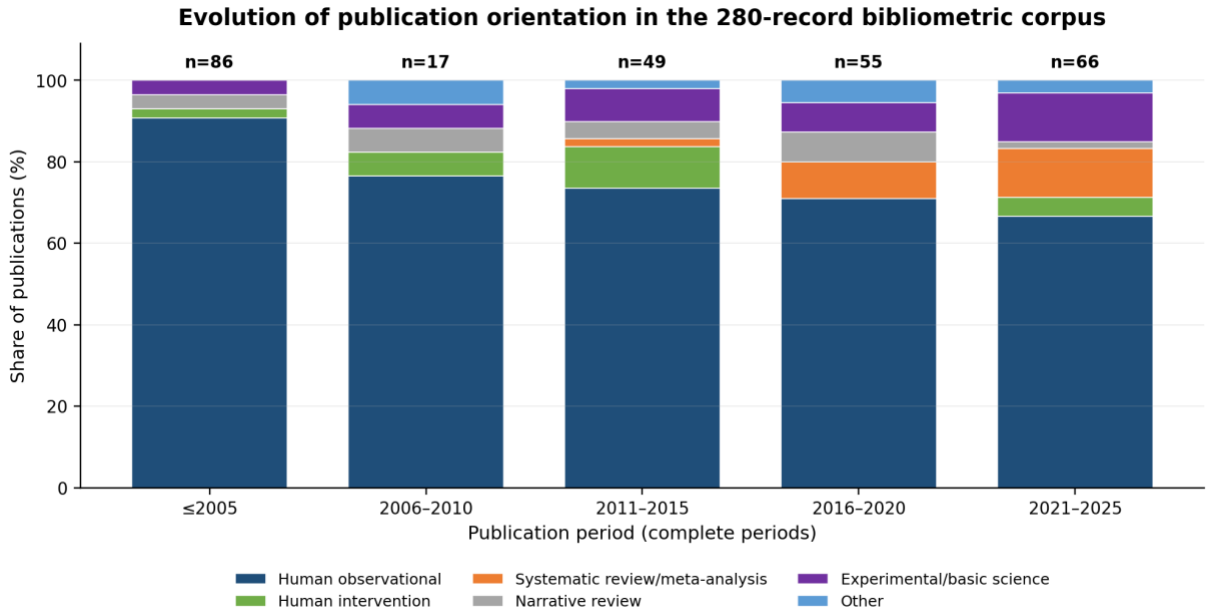

Figure 3. Evolution of publication orientation across complete publication periods in the 280-record bibliometric corpus. The seven records published in incomplete year 2026 were excluded from the period comparison.

Characteristics of the Direct Evidence

The 32 included reports were exclusively observational and represented 30 unique study populations after companion-publication consolidation. Hospital-based case-control and cross-sectional designs predominated; cohort and nested case-control studies were less common. Maternal serum and plasma were the most frequently examined matrices, while a smaller subset assessed erythrocytes or leukocytes. Only five study populations (16.7%) obtained samples prospectively or before clinical diagnosis, including first-trimester or mid-pregnancy sampling; consequently, 25 populations (83.3%) contributed predominantly post-diagnostic or otherwise non-predictive evidence. Earlier studies relied mainly on atomic absorption spectrometry, whereas recent multi-element studies increasingly used inductively coupled plasma optical emission spectrometry or mass spectrometry. Reporting of dietary intake, supplement use, inflammation, albumin or ceruloplasmin, renal function, and analytical quality control was not consistently available across studies.

Direction of Evidence by Element

Selenium was evaluated in 12 unique studies. Eight studies (66.7%) reported lower selenium or an inverse association with preeclampsia risk or severity, one reported higher selenium, and three reported no significant difference. The inverse pattern included a nested case-control study in which plasma selenium was lower among women who developed preeclampsia and the lowest tertile was associated with greater risk [16], as well as studies reporting lower maternal selenium after diagnosis [11,27,29,32,38]. However, a large early-pregnancy study did not identify an independent selenium association [28], and an Indonesian study reported higher serum selenium in severe preeclampsia [35].

Zinc was evaluated in 25 studies. Fourteen studies (56.0%) reported lower zinc, two reported higher zinc, and nine found no significant difference. Lower zinc was evident in studies from India, Korea, Venezuela, Bangladesh, Nigeria, and recent maternal-fetal analyses [9,10,22,31,32,39]. For example, the Nigerian case-control study reported markedly lower serum zinc in preeclampsia than in normotensive pregnancy [22]. In contrast, Atarod et al. observed progressively higher zinc from controls to mild and severe preeclampsia [12], while several prospective or contemporary studies reported little or no difference [19,26,28,33,37].

Copper produced the most bidirectional findings. Of 18 studies, ten (55.6%) reported lower copper, seven (38.9%) reported higher copper, and one found no significant difference. Lower copper was reported in studies from Nigeria, Tunisia, Bangladesh, Saudi Arabia, and South Africa [8,13,14,18,22-24]. Al-Jameil et al. found lower serum copper and zinc in preeclampsia than controls using ICP-OES [18], and Onyegbule et al. similarly reported reductions in both elements [22]. Conversely, copper was higher in severe disease or in prospective prediagnosis samples in several studies [11,12,17,19,20,32,36]. All three studies that explicitly assessed the Cu/Zn ratio reported a higher ratio in preeclampsia [17,20,21].

Table 3. Direction-of-evidence synthesis across unique studies.

Element	Studies, n	Lower/inverse	Higher/positive	No difference
Selenium	12	8 (66.7%)	1 (8.3%)	3 (25.0%)
Zinc	25	14 (56.0%)	2 (8.0%)	9 (36.0%)

Copper	18	10 (55.6%)	7 (38.9%)	1 (5.6%)
Cu/Zn ratio	3	0	3 (100%)	0

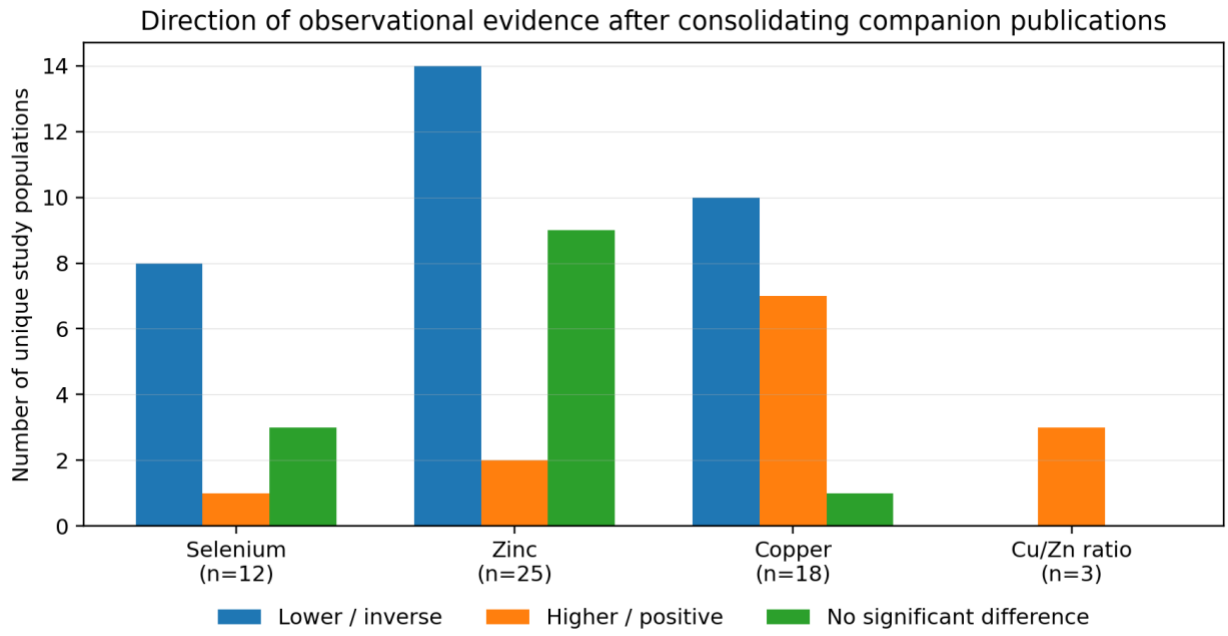

Figure 4. Direction-of-evidence synthesis for selenium, zinc, copper, and the Cu/Zn ratio across 30 unique observational study populations.

DISCUSSION

Principal Findings

This combined bibliometric analysis and evidence map shows a growing but methodologically fragmented literature. The broad bibliometric corpus comprised 280 unique records and was dominated by human observational studies (77.1%), whereas human intervention studies accounted for only 3.9%. Evidence-synthesis publications increased after 2015, but this expansion mainly reflects consolidation of existing association studies rather than a parallel shift toward prospective or interventional evidence. The direct evidence map was deliberately restricted to 32 observational full-text reports from 2006-2025. Despite increasing publication activity, the evidence remained dominated by post-diagnosis case-control and cross-sectional comparisons. The most defensible elemental pattern was lower selenium or an inverse selenium association. Zinc was more often lower than unchanged, but

the signal was not uniform. Copper was almost evenly divided between lower and higher findings, while the Cu/Zn ratio was consistently elevated in the small number of studies assessing it.

Biological Interpretation of Selenium and Zinc

The selenium pattern is biologically coherent with impaired selenoprotein-dependent antioxidant defence. Glutathione peroxidases and thioredoxin reductases limit peroxide accumulation and help maintain vascular redox balance. Several studies linked low selenium with lower antioxidant-enzyme activity or greater disease risk [16,27,30]. Nevertheless, lower selenium after diagnosis cannot distinguish a pre-existing deficiency from consumption, redistribution, altered binding proteins, or haemodilution. The three null studies and one higher-selenium study emphasize that biological matrix, population intake, gestational timing, and analytical method may modify the association.

Zinc also contributes to antioxidant defence, membrane integrity, transcriptional regulation, and placental growth. The predominance of lower findings supports a plausible relationship, but the 36% null proportion is substantial. Pregnancy itself lowers circulating zinc through plasma-volume expansion, altered albumin binding, and maternal-fetal transfer. Acute inflammation may further redistribute zinc from plasma. Consequently, a late-pregnancy case-control difference may be a marker of disease activity or nutritional vulnerability rather than a causal exposure. Prospective studies are particularly informative: some found lower concentrations before diagnosis, whereas others found no association [19,26,28].

Why Copper Findings Are Bidirectional

Copper requires a different interpretation. Most circulating copper is carried by ceruloplasmin, an acute-phase protein that rises during pregnancy and inflammation. Higher copper in preeclampsia may therefore reflect inflammatory or hepatic responses, increased ceruloplasmin, oxidative stress, or disease severity. This mechanism is compatible with prospective evidence showing modestly elevated copper before diagnosis [19] and with studies

reporting higher copper in established or severe disease [11,12,17,20,32,36]. Conversely, lower copper may reflect nutritional depletion, altered placental transfer, population-specific exposure, or assay and sampling differences [8,13,14,18,22-24]. These competing mechanisms explain why copper alone is unlikely to function as a universal deficiency marker.

The Cu/Zn ratio may integrate two opposing acute-phase changes: rising copper or ceruloplasmin and falling zinc. All three ratio studies reported higher values in preeclampsia, suggesting that the ratio deserves further prospective evaluation. However, this finding is based on only three studies and should not be interpreted as a validated diagnostic or predictive threshold.

Evidence Maturity, Translational Readiness, and Research Roadmap

The publication-orientation analysis confirms that the field is association-rich but temporality-poor. Human observational studies comprised 216 of 280 records, while only 11 publications were intervention studies. Evidence syntheses increased substantially after 2015, but this growth mainly aggregated existing association studies rather than generating causal or clinically actionable evidence. Within the direct evidence map, only five of 30 unique populations used prospective or prediagnostic sampling. Most observed concentration differences therefore cannot distinguish antecedent nutritional or environmental exposure from consequences of established preeclampsia, including inflammation, altered vascular permeability, renal dysfunction, haemodilution, and redistribution of element-binding proteins. Serial measurements beginning in the first trimester and repeated before and after clinical onset are the most important next step for establishing temporality.

The three target elements differ in translational readiness. Selenium showed the most coherent inverse pattern and is the strongest candidate for prospective dose-response validation, but repeated measurements are needed to distinguish persistent low status from disease-related consumption or redistribution. Zinc was generally lower, yet its substantial null proportion indicates sensitivity to gestational age, dietary intake, supplement use, albumin binding, inflammation, and maternal-fetal transfer. Copper should not be interpreted

as an isolated deficiency biomarker because lower and higher findings occurred with similar frequency. Future copper studies should measure ceruloplasmin, C-reactive protein or other inflammatory markers, albumin, renal function, zinc, and the Cu/Zn ratio concurrently. The consistently higher Cu/Zn ratio in three studies is promising but insufficient for a clinical threshold [17,20,21].

A second gap is inadequate preeclampsia phenotyping. Many studies treated preeclampsia as a single outcome despite probable biological differences between early- and late-onset disease, preterm and term disease, severe and non-severe presentations, and cases with or without fetal growth restriction or HELLP syndrome. Severity-stratified findings in several reports suggest that element concentrations may reflect disease stage or phenotype rather than a universal preeclampsia signal [11,12,18]. Future studies should prespecify subtype analyses and avoid combining gestational hypertension with preeclampsia unless separate results are reported.

Analytical and reporting heterogeneity further limits comparability. Serum, plasma, erythrocytes, and leukocytes represent different biological compartments; atomic absorption spectrometry, ICP-OES, and ICP-MS also differ in sensitivity and susceptibility to contamination. Multicentre studies should use metal-free collection procedures, certified reference materials, external quality assurance, harmonized units, matrix-specific pregnancy reference intervals, and transparent reporting of sample storage, haemolysis, fasting status, prenatal supplementation, dietary assessment, and gestational age at sampling. These variables should be treated as core design features rather than optional covariates.

Clinical utility remains largely untested. Most studies compared group means or reported statistical significance, while few evaluated thresholds, discrimination, calibration, incremental value beyond maternal clinical risk factors, or external validation. Trace elements should therefore be assessed as complementary markers rather than substitutes for established obstetric assessment or angiogenic biomarkers. A rational translational pathway

is: multicentre first-trimester cohort development; serial and phenotype-specific validation; externally validated prediction models; evaluation of added clinical utility; and only then biomarker-stratified supplementation or other targeted interventions. The prioritized research gaps are summarized in Table 4.

Table 4. Research gaps and prioritized future study directions.

Domain	Current evidence	Key gap	Priority study direction
Temporality	Only 5/30 populations used prospective or prediagnostic sampling.	Reverse causation and inability to distinguish cause from disease-related redistribution.	Multicentre cohorts with serial sampling from the first trimester through diagnosis.
Selenium	Most consistent lower/inverse pattern (8/12 studies).	Limited dose-response evidence and repeated measurements.	Prospective validation with serial Se and selenoprotein-related measures.
Zinc	Generally lower, but 9/25 studies reported no difference.	Confounding by diet, supplements, gestational age, albumin, inflammation, and fetal transfer.	Nutrition-adjusted longitudinal studies with standardized sampling.
Copper	Bidirectional findings: 10 lower and 7 higher among 18 studies.	Total Cu is strongly influenced by inflammation and ceruloplasmin.	Measure Cu with ceruloplasmin, CRP, albumin, renal function, Zn, and disease severity.
Cu/Zn ratio	Higher in all three studies that assessed it.	Very small evidence base and no validated threshold.	Prospective multicentre validation and comparison with Cu or Zn alone.
PE phenotype	PE often analysed as a single disorder.	Limited separation of early/late onset, severity, FGR, and HELLP.	Prespecified phenotype-stratified analyses with uniform definitions.
Analytical standardization	Multiple matrices, platforms, units, and storage procedures.	Measurement heterogeneity and possible contamination or matrix effects.	Metal-free procedures, certified reference materials, external QA, and matrix-specific reference intervals.
Confounding and reporting	Diet, supplements, inflammation, binding proteins, and renal function were inconsistently reported.	Residual confounding and limited biological interpretation.	Minimum reporting set and multivariable adjustment for nutritional, inflammatory, and clinical factors.

Domain	Current evidence	Key gap	Priority study direction
Clinical utility	Most reports focused on mean differences and P values.	Few cut-offs, AUCs, calibration analyses, or external validations.	Assess discrimination, calibration, incremental value, external validation, and decision utility.
Intervention	Only 11/280 bibliometric records were intervention studies.	Insufficient causal evidence and unclear target population.	Undertake biomarker-stratified trials only after prospective validation identifies deficient or responsive subgroups.

The geographic distribution was broad but uneven. The largest bibliometric contributors were the United States, China, the United Kingdom, Iran, Germany, and Turkey, whereas much of the direct observational evidence came from single-centre Asian and African hospital populations. Indonesia contributed ten Scopus-indexed publications, including recent erythrocyte and multi-element studies [35,38]. External validation across nutritional, ethnic, environmental, and health-system contexts is therefore essential before universal reference ranges or intervention thresholds are proposed.

Strengths and Limitations

Strengths include dual-database searching, investigator-resolved deduplication in Rayyan, explicit separation of the 280-record bibliometric corpus from the 32-report observational evidence map, systematic coding of publication orientation, a clearly defined 20-year evidence window, restriction to preeclampsia as the primary outcome, matrix-specific eligibility, consolidation of companion publications from the same cohorts, and a translational gap framework linking evidence maturity to prioritized study designs. Direction categories were based on statistically interpretable maternal serum, plasma, leukocyte, or erythrocyte results rather than merely whether an element was mentioned.

Several limitations should be considered. One eligible 2013 report was not retrieved. No formal study-level risk-of-bias assessment or certainty grading was applied, so the map describes evidence distribution and direction rather than causal effects or definitive comparative quality. Direction counting gives equal weight to small and large studies and does

not incorporate effect magnitude. Heterogeneity in eligible matrices, units, analytical methods, sampling periods, adjustment variables, and diagnostic definitions prevented defensible pooling. The research-gap analysis was based on information reported in the included publications; absence of reporting does not necessarily confirm that a factor was not considered by investigators. Publication-orientation coding relied primarily on titles, abstracts, indexed keywords, and publication-type metadata, so some older or poorly indexed records could have been misclassified. Detailed citation, affiliation, and network indicators were based on the 256-record Scopus subset because equivalent metadata were incomplete in PubMed. Finally, restricting the evidence synthesis to 2006-2025 improved contemporary relevance but excluded historically important earlier observational studies.

CONCLUSIONS

The combined bibliometric corpus demonstrates sustained and increasing interest in selenium, zinc, copper, and preeclampsia, but the field remains association-rich and temporality-poor. Evidence aggregation has advanced faster than causal testing and clinical translation. The 2006-2025 evidence map included 32 observational reports representing 30 unique study populations, only five of which used prospective or prediagnostic sampling. Selenium showed the most consistent inverse pattern and is the clearest candidate for longitudinal validation. Zinc was generally, but not uniformly, lower and requires nutrition- and inflammation-adjusted interpretation. Copper findings were bidirectional; total copper should therefore be evaluated with ceruloplasmin, inflammatory markers, albumin, renal function, zinc, and disease severity. The Cu/Zn ratio was consistently higher in three populations but remains underinvestigated. The immediate research priority is multicentre serial sampling from early pregnancy with standardized analytical procedures and prespecified preeclampsia phenotypes. Promising markers should then undergo external validation and assessment of incremental clinical utility before biomarker-stratified interventions are considered.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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DATA AVAILABILITY

The bibliographic datasets, screening log, and study-level extraction table supporting this analysis are available from the corresponding author upon reasonable request.

DECLARATION OF ARTIFICIAL INTELLIGENCE USE

This study used ChatGPT for language refinement, content summarization, and technical writing assistance during manuscript preparation. AI-assisted outputs were critically reviewed against the bibliographic databases and full-text articles by the authors. All eligibility decisions, data verification, scientific interpretations, and final conclusions were made by the authors.

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