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Maternal serum zinc level is associated with risk of preeclampsia: A systematic review and meta-analysis

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Background: Preeclampsia (PE) is a multi-organ syndrome that onsets in the second half of pregnancy. It is the second leading cause of maternal death globally. The homeostasis of zinc (Zn) levels is important for feto-maternal health.

Objective: We aimed to collect all studies available to synthesize the evidence regarding the association between maternal Zn levels and the risk of preeclampsia.

Methods: A systematic review and meta-analysis was conducted *via* searching seven electronic databases [PubMed, Web of Science, Embase, African Journals Online (AJOL), ClinicalTrial.gov, and two Chinese databases: Wanfang and Chinese National Knowledge Infrastructure, CNKI]. Studies reporting maternal serum Zn levels in pregnant women with or without preeclampsia were included. Eligible studies were assessed through Newcastle-Ottawa Scale (NOS) and the meta-analysis was performed *via* RevMan and Stata. The random-effects method (REM) was used for the meta-analysis with 95% confidence interval (CI). The pooled result was assessed using standard mean difference (SMD). The heterogeneity test was carried out using I^2 statistics, and the publication bias was evaluated using Begg's and Egger's test. Meta-regression and sensitivity analysis was performed *via* Stata software.

Results: A total of 51 studies were included in the final analysis. 6,947 participants from 23 countries were involved in our study. All studies went through the quality assessment. The pooled results showed that maternal serum Zn levels were lower in preeclamptic women than in healthy pregnant women (SMD: −1.00, 95% CI: −1.29, −0.70). Sub-group analysis revealed that geographical, economic context, and disease severity may further influence serum Zn levels and preeclampsia.

Limitations: There are significant between-study heterogeneity and publication bias among included studies.

Conclusions: A lower level of maternal Zn was associated with increased risks of preeclampsia. The associations were not entirely consistent across countries and regions worldwide.

Systematic review registration: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=337069, Identifier: CRD42022337069

KEYWORDS

zinc, Zn, trace elements, hypertensive disorder complicating pregnancy (HDCP), systematic review, meta-analysis, preeclampsia (PE)

Introduction

Preeclampsia (PE) is a multi-system disorder that onsets at 20 wks or later in pregnancy. It can affect pregnant women in many ways, such as causing hypertension, proteinuria, liver dysfunction, placental abruption, fetal growth restriction. It is a subtype of the hypertensive disorder spectrum in pregnancy, complicating around 5% of pregnancies worldwide. It remains one of the major causes of maternal, fetal and neonatal mortality, particularly in low-income and middle-income countries (LMICs) (1, 2). Despite many researchers devoted to this field, the etiology of preeclampsia is still largely unknown.

Some scholars proposed that trace elements may play a vital role in developing preeclampsia (3–5). In spite of making up <0.1% in the human body, trace elements have a disproportional function in maintaining health. Overall, evidence suggests that micronutrient imbalances are associated with various disorders (4, 6). This will be more prominent in pregnancy when maternal requirements are usually increased. Optimal supplementation can reduce a range of pregnancies complications, e.g., anemia, gestational diabetes, thyroid disorders, and miscarriage (4).

Zinc (Zn) is one of the essential trace elements. As a micronutrient, it functions as a cofactor for up to 10% of proteins in living organisms, playing a vital role in a range of biological processes in the human body (7). Zn is involved in a range of signaling pathways, e.g., Nuclear Factor Kappa B (NF-κB) signaling, and Toll-like Receptor 4 (TLR4) signaling, carrying considerable clinical implications (8, 9). Diseases such as breast cancer, tuberculosis, and cardiovascular diseases were associated with aberrant levels of serum Zn (10–12). Maternal serum Zn levels are usually measured *via* blood sampling from the maternal antecubital vein, reflecting the maternal homeostasis of Zn (13). During pregnancy, Zn exerts a key role in both maternal physiological adaptations and fetal development. The demand for Zn in fetal growth and placental function increases during the third trimester, and may lead to a lower level of Zn in maternal serum compared to healthy non-pregnant women (14). A significant lower levels of Zn may cause a series of dysfunctions in the biological process and higher risks of developing feto-maternal complications, such as gestational diabetes, preterm pre-labor rupture of membrane (PPROM), preterm birth, and low birth weight. The relationship between maternal serum Zn and preeclampsia were studied as micronutrients imbalance is believed a contributing factor of preeclampsia (3, 15, 16).

In recent years, many studies have explored the association between maternal serum Zn levels and preeclampsia, but the results were inconsistent (17–20). There are geographical, economic and ethnic differences that may explain such disagreement (21–25). In this study, we conducted a systematic review and meta-analysis, including all studies covering the maternal serum Zn levels in preeclamptic and healthy pregnant women (1) to confirm that maternal serum Zn levels were correlated with their preeclamptic risks during pregnancy; (2) to analyze any clues of how geographical locations, economic and ethnic context affect maternal Zn status.

Methods

Protocol and registration

This study followed the Preferred Reporting Item for Systematic Reviews and Meta-analysis (PRISMA) Statement. We registered at the National Institution for Health Research with the registration identifier: CRD42022337069, https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=337069

Search strategy

We searched seven electronic databases [PubMed, Web of Science, Embase, African Journals Online (AJOL), ClinicalTrial.gov, and two Chinese databases: Wanfang and Chinese National Knowledge Infrastructure (CNKI)] from the inception of the databases to May 31st 2022. Two independent reviewers (YM-Z and SJ-J) used a combination of Medical Subject Headings (MeSH) terms and free text words such as "preeclampsia or pre-eclampsia," "zinc or Zn." The Chinese databases were approached with equivalent Chinese medical terms. We have manually checked the references of all the full-text articles we had read to complement our study. There were no other restrictions. The detailed search strategies can be accessed in Supplementary Table 1.

Eligibility criteria and study selection

Studies were included if they were: (1) Observational studies that report maternal serum Zn levels in preeclamptic and healthy pregnant women; (2) the control should be healthy pregnant women instead of gestational diabetic women or non-pregnant women.

Studies were excluded if they were conference papers, editorials, reviews, systematic reviews, or interventional studies.

Study selection was performed by YM-Z and SJ-J. A third reviewer, CZ-H was to resolve any disagreement between the two in study selection.

Data extraction and quality assessment

Following data were independently extracted by two investigators (YM-Z & SJ-J): Name of the authors, year of publication, types of study design, country of the study population, the number of subjects in the studies, the mean ± standard deviation (SD) of maternal age and serum Zn level in each study. The third investigator (CZ-H) would be consulted once there was disagreement in data extraction or scoring of the quality of studies.

Case-control and cohort studies were assessed according to The Newcastle-Ottawa Scale (NOS, http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). A score between seven and nine indicates the high quality of a study. Scores ranging from four to six were considered fair quality. A score of three or less suggests that the study was poorly designed. For cross-sectional studies, we applied an adapted form of NOS for structural assessment. The scale ranged from zero to ten. A score of seven to ten indicates good quality. Four to six were considered fair, while a score of three or less was graded as poor quality (26). Rating studies were accomplished by YM-Z and SJ-J, and discussed with CZ-H once there was disagreement in evaluation.

Sub-group analysis and meta-regression

Sub-group analysis and meta-regression were conducted to evaluate the influence of geographic location, economic development, and disease severity on maternal Zn status, and their corresponding effect on risks of preeclampsia. We categorized four geographical groups primarily based on continents, but Asia was sub-divided into Asia and the Middle-East as there are huge differences in terms of demographical features between the two groups. The final groups were: Africa (Egypt, Kenya, Nigeria, South Africa, Sudan, Zambia), Asia (Bangladesh, China, India, Indonesia, Pakistan), Middle-East (Iran, Iraq, Jordan, Saudi Arabia, Turkey), and others (Australia, Brazil, Croatia, Italy, New Zealand, Poland, and the UK). From an economic perspective, we form two groups, cited from the World Bank classification (27). Group 1 is Low-income and Lower-middle-income economies (LMICs), including Bangladesh, India, Indonesia, Iran, Kenya, Nigeria, Pakistan, Sudan, and Zambia. The countries that were rated as Upper-middle-income economies and High-income economies were allocated to the second group (HMICs), which included Australia, Brazil, Croatia, China, Egypt, Iraq, Italy, Jordan, New Zealand, Poland, Saudi Arabia, South Africa, Turkey, and the UK. Disease severity was applied to those studies with inherent groups of mild and severe disease. We also inspected whether Zn levels were associated with the measurement methods, study types, or geographical locations *via* meta-regression.

Statistical analysis

This study used Review Manager 5.4.1 (The Nordic Cochrane Center, Copenhagen, Denmark) and Stata version 16.0 (StataCorp, College Station, TX, USA). The serum Zn levels were pooled by standardized mean difference (SMD) with 95% CI to assess the correlation with preeclampsia. The I^2 was used to test the heterogeneity ($I^2 \geq 50\%$ indicates significant heterogeneity), then visualized *via* the forest plot. The random-effect model (REM) was adopted to calculate the combined results if the heterogeneity is considered significant. A sensitivity analysis was performed with the removal of each study once to assess whether any single study could affect the whole outcome. Publication bias was visualized *via* funnel plot with Begg's test and tested with Egger's linear regression.

Results

Study selection

One thousand four hundred seven articles were identified after screening seven databases mentioned above. No additional studies were found after checking the references of full-text articles. One hundred fifty-five articles were excluded for duplication. One thousand one hundred eighty-two papers were further ruled out based on title and abstract. After full-text checks, another 19 articles were excluded for the following reasons: (1) Nine were excluded for not answering the research questions; (2) Three were excluded for improper comparison; (3) Two were excluded for improper study types; (4) Five were excluded for inaccessible data. Fifty-one studies were left for quality assessment and data extraction (13, 21–25, 28–72) See Figure 1.

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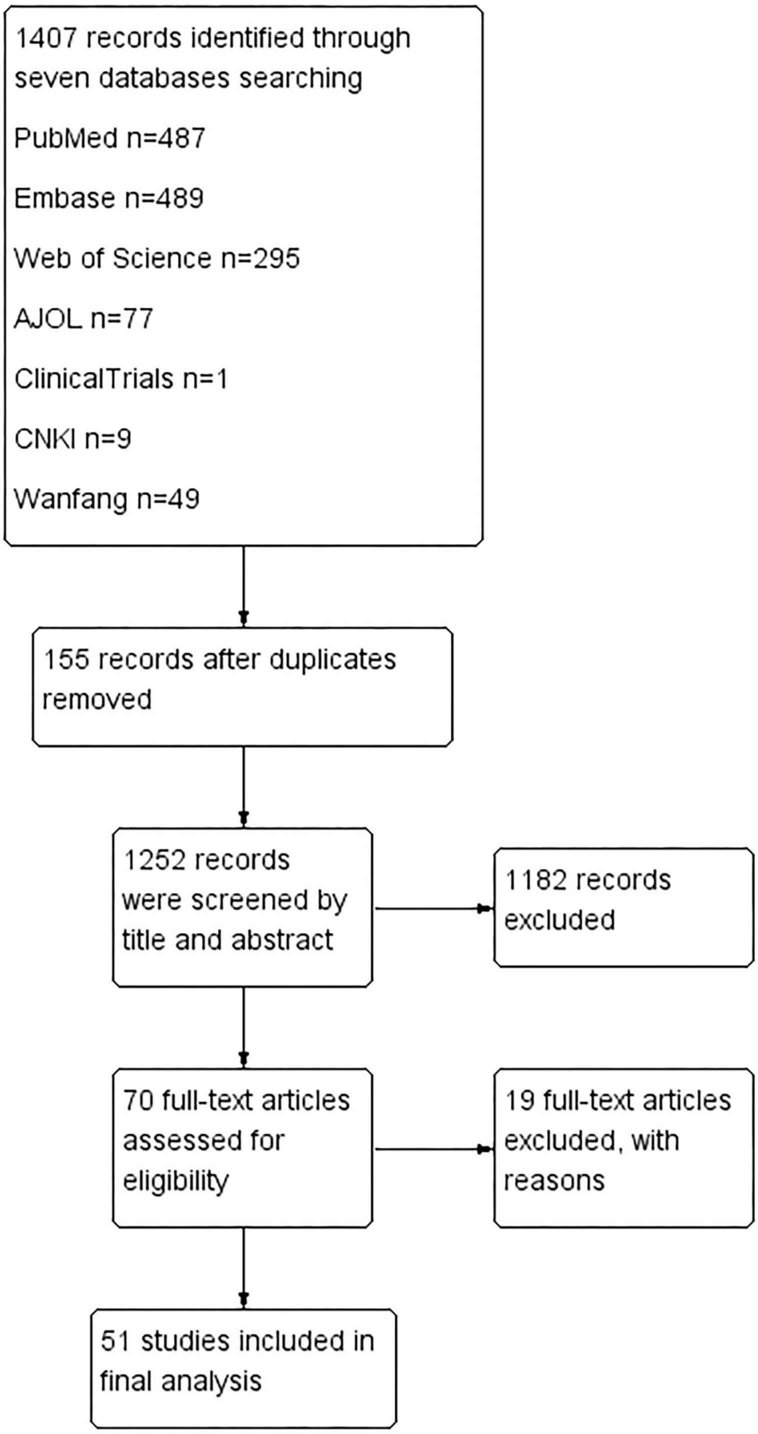

FIGURE 1
PRISMA flow diagram for study selection process.

Basic features of included studies

The 51 studies were conducted across 23 countries over a period of 32 years (1990–2022). Fourty-one studies were case-control, seven were cross-sectional and three were cohort studies. The numbers of preeclamptic women in a single study ranged from 14 to 427 (21, 67) Although not clearly stated in some articles, there was no significant difference in age between the preeclampsia group and the control (21, 30, 37, 39, 40, 46–48, 51, 52, 63, 72). Maternal serum Zn levels were most frequently measured *via* atomic absorption spectrophotometer (AAS) or flame atomic absorption spectrophotometer (FAAS). Other details can be found in Supplementary Table 1.

Results of systematic review

All studies were classified according to their study designs and further assessed *via* NOS quality assessment tools. Thirty-six (3 cross-sectional, 3 cohort studies and 30 case-control studies) articles were rated as high quality after structured evaluation, while 15 were rated as fair qualified. Detail scores can be accessible in Supplementary Tables 2.1–2.3.

Results of meta-analysis

The total number of preeclamptic women involved in this research was 3,162, while the number of participants in the control group was 3,785. The pooled result showed that maternal serum Zn level in preeclamptic women was lower than in healthy control (SMD: −1.00, 95% CI −1.29, −0.70, see Figure 2). The funnel plot can be seen in Figure 3. Begg's test and Egger's test were also performed to assess publication bias, and significant bias was discovered ($z = 2.88$, $p = 0.004$; $t = -3.89$, $p = 0.000$; Supplementary Figure 1). Sensitivity analysis demonstrated that no single study had an overall influence (Supplementary Figure 2; Supplementary Table 3).

Results of meta-regression

The heterogeneity between studies and across sub-groups was significant. Meta-regression was then performed to explore possible causes. The method of measurement, the geographical locations and the designs of the study types were assessed but the results revealed that the geographical location, study type and different measurement methods were not the causes for heterogeneity (the *P*-value were 0.399 for geographical location, 0.864 for study type, 0.277 for measurement, respectively). Detailed results can be seen in Supplementary Figures 3A–C.

Results of sub-group analysis

Sub-group analysis from a geographic view

Africa has seen the largest number of recent studies. All 12 studies were published since 2010, with 1,465 participants involved. The pooled result was non-significant (SMD −0.65, 95% CI: −1.52, 0.21). Asia is currently home to the largest number of studies and participants (20 studies with 2,665 pregnant women involved), and the result was generally consistent between studies and revealed a negative significance (SMD −1.60, 95% CI −2.13, −1.07). In the Middle-East region, the maternal serum Zn levels were also consistently lower in preeclamptic women compared with normotensive pregnant women, but the difference were not as significant as the population in Asia (SMD −0.93, 95% CI −1.36, −0.49 vs. −1.60, −2.13, −1.07 in Asia). The rest studies were primarily from Europe: one from Italy, one from Croatia, one from Poland, one from Australia, one from Brazil, and one from multi-centers in the UK, Australia and New Zealand. The results were non-significant (SMD 0.02, 95% CI −0.14, 0.18). More detailed results were available in Supplementary Figure 4.

Sub-group analysis from an economic view (HIMCs vs. LMICs)

The studies were divided into High-and-Upper-middle-Income countries (HIMCs, 29 studies from 13 countries were included) and Low-and Lower-middle-Income countries (LMICs, 22 studies from 10 countries were included) from an economic perspective. The pooled results of SMD were −0.84 in HMICs vs. −1.23 in LMICs, respectively. The negative association of maternal Zn levels was more notable in developing countries with details accessible in Supplementary Figure 5.

Disease severity and Zn levels

Only ten studies have sub-divided the disease of preeclampsia into mild and severe types. The pooled results demonstrated that maternal Zn levels were more negatively associated with disease severity. The SMD was −0.75 (95% CI: −1.36, −0.15) in mild preeclamptic women and −1.32 (95% CI: −2.02, −0.63) in severe form. Other details can be seen in Supplementary Figure 6.

Discussion

This systematic review and meta-analysis mainly focus on whether there is an association between maternal serum Zn levels and preeclampsia. The overall result demonstrates that a lower level of maternal serum Zn was observed in preeclamptic women than in normotensive pregnant women worldwide. The trend was more prominent in Asian ethnicity, low-income economies and severe patients. This is generally consistent with findings from other reports (17–20).

Zn has many roles in the body, including maintaining the catalytic activity of a range of enzymes, protein synthesis, cell division. It is also involved in the immune system, nerve function, and fertility (4). Its role in the immune system has been well-known for several decades (73). T-lymphocytes activation requires the presence of Zn. Even a mild degree of

 10.3389/fpubh.2022.968045

Study or Subgroup	PE Mean	PE SD	PE Total	Healthy pregnant control Mean	Healthy pregnant control SD	Healthy pregnant control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Adam 2001	31.3	4.7	20	34.1	4.4	20	1.9%	-0.60 [-1.24, 0.03]
Ahsan 2013	0.016	0.002	44	0.015	0.002	27	2.0%	0.49 [0.01, 0.98]
Akhtar 2011	902.5	157.15	60	1,153.33	67.09	30	2.0%	-1.85 [-2.37, -1.33]
Akinloye 2010	8.6	1.4	49	9.4	0.8	40	2.0%	-0.68 [-1.11, -0.25]
Al-Jameil 2014	0.67	0.59	40	1.3	0.83	40	2.0%	-0.87 [-1.33, -0.41]
Al-Sakarneh 2021	63.71	1.24	30	65.37	1.27	30	1.9%	-1.31 [-1.87, -0.74]
Al-Shalah 2016	57.28	13.48	60	87.54	28.74	60	2.0%	-1.34 [-1.74, -0.94]
Atamer 2005	0.79	0.18	32	1.09	0.2	28	1.9%	-1.56 [-2.15, -0.98]
Bai 2013	6.99	0.73	77	8.96	0.63	56	2.0%	-2.84 [-3.33, -2.35]
Bakacak 2015	81.24	12.06	38	108.45	0.63	40	1.9%	-3.20 [-3.88, -2.52]
Borella 1990	10.49	2.28	24	9.6	2.29	35	2.0%	0.38 [-0.14, 0.91]
Brito 2013	43.89	10.34	44	48.3	8.3	50	2.0%	-0.47 [-0.88, -0.06]
Chababa 2018	89.17	47.19	41	76.2	35.23	57	2.0%	0.32 [-0.09, 0.72]
Desouky 2020	60.8	12.8	25	95.7	10.4	25	1.8%	-2.95 [-3.76, -2.13]
El-Moselhy 2010	60.81	9.74	100	95.7	12.41	100	2.0%	-3.12 [-3.53, -2.70]
Elmugabil 2016 (1)	108	29.7	50	102	30.5	50	2.0%	0.20 [-0.20, 0.59]
Enebe 2020	0.41	0.39	81	0.54	0.8	81	2.0%	-0.21 [-0.51, 0.10]
Farzin 2012	76.49	17.62	60	100.61	20.12	60	2.0%	-1.27 [-1.66, -0.87]
Feng 2013	0.86	0.23	30	0.98	0.21	30	2.0%	-0.54 [-1.05, -0.02]
Fenzl 2013	9.23	1.43	30	8.85	1.43	37	2.0%	0.26 [-0.22, 0.75]
Gan 2019	10.3	2.98	33	13.44	2.33	23	1.9%	-1.13 [-1.71, -0.56]
Gao 2020	6.33	1.75	427	6.49	1.84	427	2.1%	-0.09 [-0.22, 0.05]
Gul 2022	75.1	20.9	43	80.3	17.7	45	2.0%	-0.27 [-0.69, 0.15]
Guo 2013	58.9	6.51	46	68.77	9.33	40	2.0%	-1.23 [-1.69, -0.77]
Gupta 2014	9.28	1.63	75	10.63	1.82	75	2.0%	-0.78 [-1.11, -0.45]
Harma 2004	15.53	4.92	24	11.93	3.11	44	2.0%	0.93 [0.40, 1.45]
Hassan 2014	49.4	17	122	90.3	16.8	79	2.0%	-2.41 [-2.78, -2.04]
Ikaraoha 2016	45.8	9.7	59	68.2	10.1	150	2.0%	-2.23 [-2.60, -1.86]
Ilhan 2002	82.94	28.93	21	125.19	24.23	30	1.9%	-1.58 [-2.23, -0.94]
Jain 2010	12.38	1.55	50	15.64	2.4	50	2.0%	-1.60 [-2.05, -1.15]
Jamal 2017	2.94	0.45	40	5.11	0.21	40	1.6%	-6.12 [-7.19, -5.05]
Ji 2010	67.42	13.48	37	66.45	12.45	80	2.0%	0.08 [-0.31, 0.47]
Kanagal 2014	8.84	0.87	60	14.87	0.89	60	1.7%	-6.81 [-7.75, -5.86]
Keshavarz 2017	0.69	0.21	100	0.87	0.3	100	2.0%	-0.69 [-0.98, -0.41]
Kolusari 2008	1.06	0.44	47	1.27	0.41	48	2.0%	-0.49 [-0.90, -0.08]
Lewandowska 2019	615.4	83.6	121	614.6	93.75	363	2.1%	0.01 [-0.20, 0.21]
Li 2009	7.04	1.27	62	8.91	0.6	28	2.0%	-1.67 [-2.18, -1.16]
Lu 2016	6.94	1.13	60	8.93	0.54	30	1.9%	-2.02 [-2.55, -1.49]
Maduray 2017 (2)	18.03	30.28	43	2.13	3.01	23	2.0%	0.64 [0.12, 1.16]
McKeating 2021	526.93	111.59	44	510.15	175.7	193	2.0%	0.10 [-0.23, 0.43]
Memon 2017	0.71	0.04	40	0.88	0.02	40	1.7%	-5.32 [-6.28, -4.37]
Mistry 2015	579.78	87.63	244	577.77	93.77	472	2.1%	0.02 [-0.13, 0.18]
Onyegbule 2016	12.26	1.83	54	8.27	0.6	48	1.9%	2.84 [2.28, 3.40]
Pulei 2018	9.9	3.7	54	10.7	3.5	54	2.0%	-0.22 [-0.60, 0.16]
Rafeeinia 2014	0.71	0.26	50	0.73	0.33	50	2.0%	-0.07 [-0.46, 0.33]
Rathore 2011	49.2	17.8	14	57.5	21.6	47	1.9%	-0.39 [-0.99, 0.21]
Samar 2020	85.43	12.07	50	91.79	9.02	52	2.0%	-0.59 [-0.99, -0.20]
Sarwar 2013	0.77	0.35	50	0.98	0.23	58	2.0%	-0.71 [-1.11, -0.32]
Ugwuja 2010	9.97	9.74	40	10.87	10.28	40	2.0%	-0.09 [-0.53, 0.35]
Yang 2007	0.71	0.17	47	0.77	0.16	30	2.0%	-0.36 [-0.82, 0.10]
Yusrawati 2017	4.8	2.62	70	5.5	3.53	70	2.0%	-0.22 [-0.56, 0.11]
Total (95% CI)			**3162**			**3785**	**100.0%**	**-1.00 [-1.29, -0.70]**

Heterogeneity: Tau² = 1.08; Chi² = 1476.60, df = 50 (P < 0.00001); I² = 97%
Test for overall effect: Z = 6.66 (P < 0.00001)

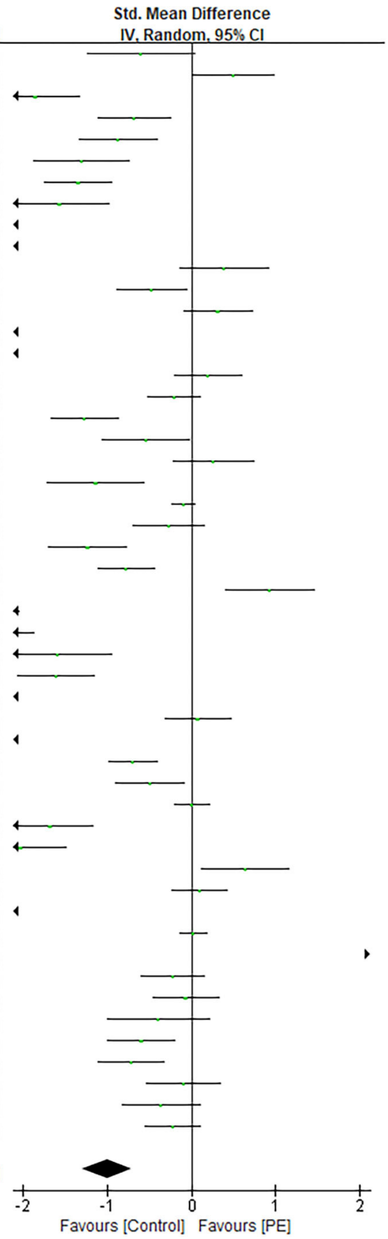

FIGURE 2
The forest plot for correlation between maternal serum Zn levels in preeclamptic women and healthy pregnant women.

Zn deficiency can impair macrophage, neutrophil functions, natural killer (NK) activity and complementary response (74). It also helps maintain skin integrity and delay age-related macular degeneration, and vision loss (75, 76). Zn level mainly depends on dietary intake as no specific Zn storage system has been identified (77). The Recommended Dietary Allowance (RDA) of Zn for pregnant women in the US is at least 11 mg/d. Oysters, red meat like beef, poultry, and beans are zinc-rich diet choices. A higher level of zinc-containing supplements may bring more benefits (4). Zn-containing supplements are additional resources for Zn intake. The median level of Zn is 15 mg in prenatal supplements in the US markup-to-datedate evidence suggests zinc sulfate, zinc gluconate or zinc lactate may be beneficial, while zinc acetate should be avoided (4). Despite the maternal serum levels of Zn can be influenced by confounders such as stress and infections, Zn toxicity barely occurs in women with an average daily intake of zinc-containing supplements or food (16). The Tolerable Upper Limit (TUL) is 40 mg daily.

During pregnancy, Zn is essential in embryogenesis and fetal development. Animal studies have shown that Zn deficiency

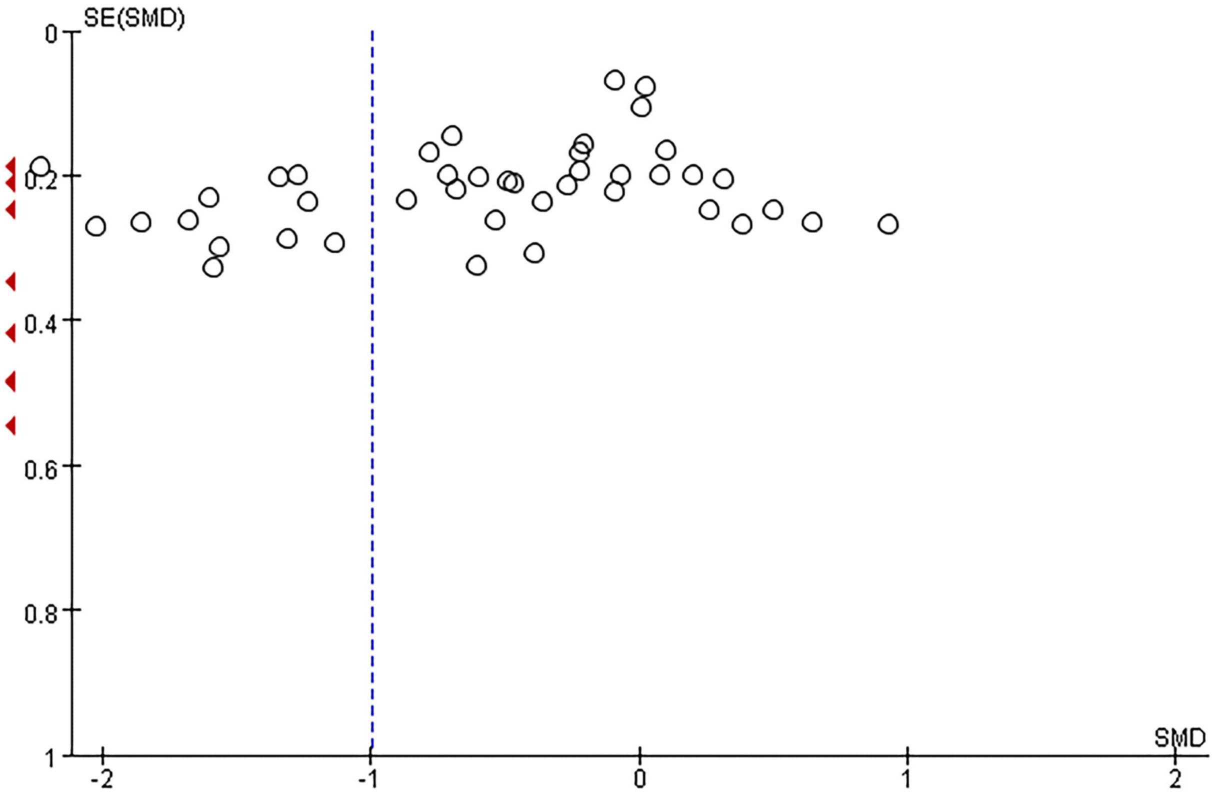

FIGURE 3
The funnel plot to assess publication bias.

could lead to abnormal placental morphogenesis, which is one of the presumptive etiology of preeclampsia (78, 79). Despite being minimal in serum, the Zn level is consistently lower in preeclamptic women. This indicates that Zn has a role to play in the pathogenesis of this pregnancy-specific disorder. There are studies suggest Zn as an antioxidant trace element, can relieve the oxidative stress in rats (78, 80). Oxidative stress is believed one of the key pathogenesis in the development of preeclampsia. A more recent study has identified that Zn may also participate in ferroptosis, a newly-discovered iron-dependent form of non-apoptotic cell death (81, 82). Furthermore, as there has been no solid evidence to demonstrate a preventive effect of Zn supplements to reduce the risk of preeclampsia, clinical research can be conducted to explore the possibility that Zn takes part in ferroptosis to mediate the development of preeclampsia (83).

Despite four meta-analysis having reached similar conclusions that maternal serum Zn levels were lower in preeclamptic women, there were reasons why we updated the evidence and added more information (17–20). (1) Three meta-analysis were conducted before 2016, but 20 articles we had included were after that (21–24, 32, 39, 41, 42, 46, 51, 54, 57, 60–65, 68, 72). This indicates there are still unclear or unreasonable phenomena and different conclusions may be drawn with more evidence accumulated and careful analysis. (2) The other meta-analysis, conducted last year focused on the African population while we have a global perspective. By comparison, we give more information for researchers who also care about the rest of the world. (3) All the four meta-analysis did not include adequate articles even in their claimed scope. We found more than 30 studies reporting a relationship between maternal Zn levels and preeclampsia by 2016 using almost the same search strategy as Zhu et al. (17, 18, 20). We had involved one more African study compared to Tesfa et al. (61) (4) We have the most complete sub-group analysis. Zhu et al. had sub-group analysis in terms of study design and geographical locations, but they only include a total of 13 studies (20). Ma et al. revealed a sub-group analysis in terms of continent (Asia, Europe, Africa), sample type (plasma, serum), fasting status (yes or no), individual age match or gestational age match) (18). These results of sub-group analysis may be extrapolated cautiously as the number in each group was relatively small. He et al. did not involve sub-group analysis (17). In general, we have synthesized the most up-to-date evidence, applied sub-group analysis to identify more information to encourage further research.

However, our studies have several limitations. First, we claim to have a global view, but there was scanty evidence from Latin America or some non-English speaking European countries. This is due to that we have not searched the non-English databases. However, we have involved all the possible database we can have, including a pure African database and two Chinese databases to complete a global view. The English language accounts for most world's existing research articles, and we did not preclude non-English literature in the major database (i.e., PubMed, WOS, Embase). Therefore, we believe that we are very near to all the related literature available in the world. Second, only six western countries were included in our studies. This is less convincing to draw a global conclusion without obtaining enough evidence from an important part of the world (23, 25, 37, 45, 62). This may also reflect that the micronutrients have not been a focus in developed countries anymore as there is scarce research currently conducted in conventional western countries. Third, the between-study heterogeneity was significant even though we had considered different definitions of preeclampsia, different methods of measurement, participants' fasting status, and various conditions for storage. However, it was also reflected in other similar meta-analysis covering the correlation between trace elements or vitamins and preeclampsia (84–86).

Conclusion

In summary, we have confirmed that maternal serum Zn levels are negatively associated with preeclamptic risk. This correlation is more prominent in Asian countries and low-income economies and is also inversely related to the severity of preeclampsia. Well-designed large cohort or interventional studies in the future may explore why and how maternal serum Zn levels affect the risk of preeclampsia.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

SJ and YZ: conceptualization, methodology, software, investigation, resources, project administration, modification, and writing back to reviewers. SJ and CH: validation, formal, analysis, and data curation. SJ: writing original draft preparation. CH: writing review, editing, and supervision. YZ: visualization and funding acquisition. All authors have read and agreed to the published version of the manuscript.

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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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.968045/full#supplementary-material

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