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Systematic Review

Maternal Blood Trace Element Levels in Preeclampsia: Comprehensive Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: Deficit in trace elements was frequent in pregnant women and could lead to preeclampsia development. This meta-analysis aimed to determine calcium, magnesium, zinc, iron, and copper serum levels in preeclampsia women compared to healthy pregnant women.

Methods: A systematic search is conducted in PubMed, ScienceDirect, and Google Scholar from inception into March 25th, 2022 using keywords of "("calcium" OR "magnesium" OR "zinc" OR "copper" OR "iron" OR "trace element" OR "trace elements") AND ("serum" OR "blood") AND ("preeclampsia")". Articles obtained from PubMed, ScienceDirect, and Google Scholar were 62, 31, and 119 respectively. The article screening process was based on the PRISMA 2020 guidelines. Study quality was assessed using NOS.

Results: Fifty-four studies were included in this systematic review. Pooled analysis revealed that serum calcium (SMD = (-1.66; 95% CI = -2.05 to -1.28, magnesium (SMD = -1.28; 95% CI = -1.37 to -1.20, and zinc were significantly lower in preeclampsia (SMD = -2.4; 95% CI = -4.11 to -0.7. Serum iron was higher in preeclampsia (SMD = 1.71; 95% CI = 0.21 to 3.21). No significant different difference in serum copper level.

Conclusion: The mean blood levels of calcium, magnesium, and zinc were considerably lower, while blood iron levels were higher in preeclamptic women compared to the healthy pregnant group. Copper levels were not significantly different between the two groups.

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INTRODUCTION

Preeclampsia is a multi-organ disorder of pregnancy that develops after 20 weeks of gestation, characterized by newly diagnosed hypertension accompanied by proteinuria [1]. Despite the ongoing study, the cause of this illness remains unknown, and placental delivery remains the only treatment option [2]. Preeclampsia is thought to be caused by aberrant placentation, widespread endothelial cell dysfunction, and elevated systemic inflammation, according to evidence from animal and human research [3]. Trace element deficits are frequent in pregnant women and can lead to the development of preeclampsia [4].

Rarely reported in the scientific literature, the status of trace elements in pregnant women relies on reports of trace element deficits. The plasma level at recruitment demonstrated that 25.6% of pregnant women had hypocalcemia (8-20 weeks) [5]. Up to 52 percent of pregnant women worldwide suffer from iron deficiency [6]. Zinc has been the most studied because it may be associated with low birth weight and hypertensive pregnancy disorders [7].

Trace elements are essential for metabolism and tissue function preservation. They are an essential component of a powerful antioxidant that protects the cell from harm [8]. Several anomalies in essential trace elements (Calcium, Magnesium, Zinc, Iron, and Copper) have been proposed to have a role in preeclampsia [4]. However, studies examining the

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relationship between serum Zinc, Copper, Magnesium, Calcium, and Iron to preeclampsia differed widely.

Therefore, academics, public health, and clinicians must prioritize research on trace elements and preeclampsia. The findings of studies on trace elements and preeclampsia provide evidence-based recommendations for preeclampsia prevention, such as calcium and zinc supplementation [9]. The goal of this study was to look at the levels of blood calcium, Magnesium, Zinc, Iron, and Copper in preeclampsia and see if they could have a role in the etiology/ pathogenesis of the disease, as well as to add to prior studies on preeclampsia throughout the world.

MATERIAL AND METHODS

Registration and Protocol

We registered our review protocol on PROSPERO, the International Prospective Registry of Systematic Reviews with ID number CRD42022340679. The entire protocol can be accessed through https://www.crd.york.ac.uk/prospero.

Literature Searching

We want to determine the association between maternal blood trace element levels and preeclampsia. The following databases were combed; PubMed, ScienceDirect, and Google Scholar. Medical Subject Heading (MeSH) phrases were used in the search: "("calcium" OR "magnesium" OR "zinc" OR "copper" OR "iron" OR "trace element" OR "trace elements") AND ("serum" OR "blood") AND ("preeclampsia")" individually or in combination. All past 10 years publications until March 25th, 2022, were retrieved and appraised for inclusion in this review. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 guidelines [10].

Eligibility Criteria

The following were the study's inclusion criteria:

1. Observational study (case control, cross sectional, and cohort study)
2. Studies within the last ten years
3. Subjects were pregnant preeclamptic women, diagnosed based on ACOG guidelines, as the case group dan healthy non-comorbid pregnant woman as the control group.
   We collected publications with preeclampsia criteria from the 2020 ACOG guidelines; both publications that explicitly state that the diagnosis of preeclampsia is based on ACOG guidelines or without stating that they used ACOG criteria but explain in detail by the operational definitions used in the enforcement of preeclampsia in their subjects and then we matched them with ACOG criteria for the diagnosis of preeclampsia.
4. The blood sample was venous blood drawn at a period when the woman was in the early, middle, or late stages of pregnancy.
5. Measuring outcomes are maternal serum total calcium and/or magnesium and/or zinc and/or copper, and/or iron levels.

However, the exclusion criteria include:

1. Experimental study
2. Review articles/case reports/case series, and conference abstract
3. Study with irrelevant titles/abstract
4. No full text available
5. Language other than English
6. The serum trace elements level data were more than ten times the highest limit value or ten times lower than the lowest limit value.
7. The unit of measurement is not mentioned/ incomplete data.

All studies assessed by these eligibility criteria will be compiled as a whole, and we grouped them according to the type of trace elements measured in each study. We categorized all studies into calcium, magnesium, copper, iron, and zinc groups for separate data synthesis.

Study Selection and Screening

RefMan was used to export all of the citations found by our search approach, and duplicate articles were identified using the conditional formatting tool from Microsoft Excel and deleted manually. After that, all reviewers (WH and AJ) independently examined the titles and abstracts to assess relevant studies. Prior to data extraction, the entire texts of relevant studies were obtained and extensively studied to determine their eligibility. If the reviewers could not agree, a consensus was held.

Study Quality Assessment

Study quality was assessed with Newcastle-Ottawa Scale (NOS) for case-control design and a modified version of NOS for cross-sectional design. Six points were classified as "Good," 4 to 5 points were "Fair," and 3 points were "Poor". We did not use poor-quality studies to maintain the quality of the meta-analysis in this study. The mean value of NOS was taken from 2 reviewers (WH and AJ) who had independently assessed the NOS of each study.

Data Extraction

The following data were taken from the RefMan files:

1. First author name
2. Publication year
3. Country

The following data were taken from the methodology section by the reviewers independently:

1. Preeclampsia status.
   Preeclampsia, a potentially harmful pregnancy complication marked by elevated blood pressure,

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typically manifests after 20 weeks of pregnancy. For both mother and baby, this may result in significant, even deadly, consequences. To diagnose preeclampsia, ACOG recommends the following diagnostic criteria [1]:

a. Systolic blood pressure (SBP) of ≥140 mm Hg or diastolic blood pressure (DBP) of ≥ 90 mm Hg on two occasions at least 4 hours apart after 20 weeks of gestation in a woman whose blood pressure has previously been normal
b. SBP ≥ 160 mm Hg or DBP ≥ 110 mm Hg was confirmed within a short interval (minutes) to facilitate timely antihypertensive therapy.
   AND
c. Proteinuria: greater than or equal to 300 mg per 24-hour urine collection (or this amount extrapolated from a timed collection
   OR
d. Protein/creatinine ratio ≥ to 0.3.
   OR
e. Dipstick reading of 1+ (used only if other quantitative methods are not available)
   OR
f. In the absence of proteinuria, new-onset hypertension with any preeclampsia complications.

2. Maternal trace elements serum level was presented as mean ± standard deviation. All eligible studies will measure total serum calcium, magnesium, copper, iron, and zinc instead of ionized/free form levels. Data for calcium were collected in mg/dl, magnesium in mg/dl, copper in µg/dl, iron in µg/dl, and zinc in µg/dl. If the unit of measurement is in different units, conversion is carried out with a standardized formula to achieve the same unit of measurement. Suppose the data is presented in the median; we will convert it to mean if applicable, in this case, if they have normal data distribution as seen from the standard deviation value compared to the mean. If the standard deviation is greater than the mean, then changing the median to the mean form is impossible, so that we will exclude it from the data synthesis.
3. Study design. Eligible studies can be in the form of case-control, retrospective or prospective cohort, or cross-sectional studies.
4. Subject age range.
5. Gestational age range.
6. The biochemical method was used.

Statistical Analysis

We tabulate selected studies in Microsoft Excel for each trace element. Statistical analysis was done using Review Manager (RevMan) v.5.4 to analyze the power of the association between blood trace elements level and PE using standardized mean difference (SMD) with 95% CI. To measure heterogeneity, the I^2 was utilized. Low heterogeneity was defined as I^2 of 25%, moderate heterogeneity as 25%–75%, and high heterogeneity as $I^2 > 75\%$. A random-effects model was used if there was high heterogeneity in the research population. A p-value of < 0.05 is considered significant. If appropriate and sufficient studies were available, a subgroup analysis based on race was conducted to examine the potential factors that might significantly influence between-study heterogeneity.

Publication Bias

If the meta-analysis contained more than ten papers, publication bias was visually examined using a funnel plot to eliminate the small-study impact. If not, an influence analysis was conducted, with each study removed one at a time to see if a single study significantly influenced the results.

RESULTS

Overview of Literature Searching

There were 212 studies identified through database searching from PubMed, ScienceDirect, and Google Scholar. After removing duplicates, we screened 173 titles and abstracts, leaving the 54 studies to be selected and analyzed for qualitative synthesis—Fig.1. Quantitative synthesis was done on 32 studies for calcium, 24 studies for magnesium, nine studies for copper, seven studies for zinc, and eight studies for iron.

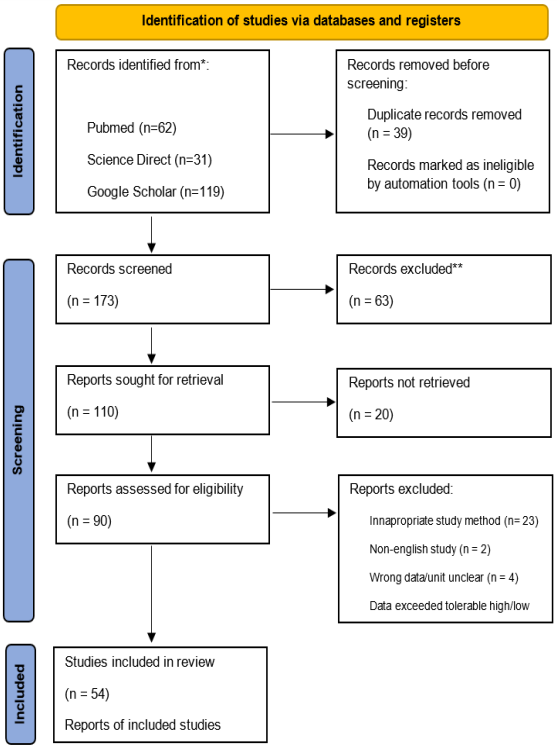


Fig. 1. PRISMA flowchart of the literature selection [10]

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Study Characteristics

In this review, 54 studies were included. A total of 4746, 3359, 2847, 598, and 561 participants were enrolled in the study of Calcium, Magnesium, Copper, Zinc, and Iron, respectively. The characteristics of the studies included are shown in Table 1.

Summary SMD for Trace Elements and the Subgroups

The levels of trace elements in preeclamptic and normal control groups were compared in this study, as seen in table 2. Calcium, Magnesium, Zinc, and Iron serum level was different between PE groups and in control ($p<0.05$).

Calcium and Preeclampsia

Of the 32 studies in the meta-analysis of calcium and preeclampsia, five studies [14,21,27,28,32] did not show significant differences between PE and control groups, while 27 other studies [4,12,23–26,29–31,33–35,13,36–41,63,64,15–20,22] showed significant differences. The blood levels of calcium are significantly lower in preeclamptic women than in normotensive pregnant women with SMD of −1.69 (95% CI −2.07, −1.31; I2 98%; $p<0.00001$). Strong evidence of study heterogeneity for serum calcium and PE, as shown in figure 2. From racial subgroup analyses, the pooled SMD were significant in studies conducted among Asian populations and African populations. A funnel plot was created and demonstrated symmetry showing no evidence of publication bias, as seen in Fig. 3.

Magnesium and Preeclampsia

Of the 24 studies included in the analysis, four studies [14,20,21,50] did not show significant differences in serum calcium levels in the PE and control groups. Two studies [41,46] reported significant differences with higher Mg levels in the PE group, while the remaining 18 studies [11–13,18,19,25,26,31,34,35,37,40,42–44,47–49,] reported significant differences with lower Mg levels in the PE group. From the pooled SMD, the blood levels of magnesium are significantly lower in preeclamptic women than in normotensive pregnant women with SMD of −1.60 (95% CI −2.23, −0.97; I^2 98%; $p<0.00001$). Strong evidence of study heterogeneity for serum magnesium and PE is shown in figure 4. Clinical variations and methodological problems, such as the sample/kit/reagent utilized in the study, may be the reason for this substantial statistical heterogeneity.

From racial subgroup analyses, the pooled SMD were significant in studies conducted among Asian populations, African populations, and European populations. The result of pooled SMD among races was significant; indicating that magnesium level was lower PE group than control group. Funnel plot was created and demonstrated symmetry showing no evidence of publication bias in this analysis as seen in Fig. 5.

Copper and Preeclampsia

Out of the nine studies included in this meta-analysis, three studies [54,56,57] did not show significant differences in serum copper levels in the PE and control groups. Four studies [21,32,52,55] showed significant differences with higher copper levels in the PE group, and two studies [51,53] reported significant differences with lower copper levels in the PE group. From the pooled meta-analysis, maternal serum copper levels were not significantly different in preeclampsia compared to healthy controls. We tested these results by eliminating related papers, and the results were consistently insignificant. However, eliminating paper Rafeeinia, Arash et al. 2014 resulted in a p-value of 0.05.

Zinc and Preeclampsia

Out of the seven studies in this analysis of zinc and preeclampsia, two studies [29,52] reported no significant differences between the PE and control groups. Four studies [21,32,53,55] showed a significant difference with lower zinc levels in the PE group, and 1 study [58] reported a significant difference with higher zinc levels in the PE group. From the pooled meta-analysis, the blood levels of zinc are significantly lower in preeclamptic women with SMD of −2.40 (95% CI −4.11, −0.70; I^2 98%; $p<0.00001$) compared to healthy control. We removed one study at a time to examine the sensitivity. No single study influenced the overall SMD result except for Mudher et al. study, meaning that it greatly influenced the meta-analysis result.

Iron and Preeclampsia

Out of the eight studies included in this meta-analysis determining the association of iron and preeclampsia; two studies [59,65] did not show a significant difference between PE and control groups, and two studies [21,29] showed a significant difference with lower iron levels in the PE group. Four studies [53,60–62] reported a significant difference with higher iron levels in the PE group. The pooled meta-analysis showed that the blood iron in preeclampsia was significantly higher with an SMD of 1.71 (95% CI 0.21, 3.21; I^2 98%; $p=0.03$) compared to healthy control. Excluding a study by Ghosh, Lipika et al. 2017 and Mudher, Haydar et al. 2015 resulted in an insignificant overall SMD with a p-value of 0.87, meaning that both studies have significant influence hence the publication bias is high.

DISCUSSION

Women of reproductive age are susceptible to both macro- and micronutrient deficiencies, with the risk

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being greater for pregnant women due to the increased demand for minerals such as zinc, copper, calcium, and vitamins to satisfy the needs of the developing fetus. [66]. Several metabolic processes use trace elements that are essential. Catalysts in chemical reactions and structural components in large molecules, such as enzymes and hormones, are among their specialised and vital functions. Changes in the concentrations and homeostasis of each of these micronutrients are well-recognized pathophysiologic factors to a wide range of illnesses and diseases [67].

Preeclampsia and eclampsia etiologies remain unidentified despite numerous researches [68]. Changes in blood trace element levels in preeclamptic individuals have been linked to the pathophysiology of this condition in some investigations [69], while others have shown no link [8]. In addition, oxidative stress is thought to have a role in the development of preeclampsia [70]. Preeclampsia is hypothesized to be caused by a malfunction in the complement system's control. Blood pressure can be affected by changes in serum trace element concentrations such as Ca, Mg, Zn, Fe, and Cu.

According to this study, the mean blood levels of Calcium and Magnesium were consistently lower in the PE group compared to the normal control accoss racial subgroup. This suggests that they might play a role in preeclampsia pathogenesis. Vasodilator effects of blood Ca and Mg on the blood arteries of pregnant women have been reported [71]. Low Ca and/or Mg levels in the blood cause vascular smooth muscle constriction, increased vascular resistance, and elevated blood pressure [72]. Magnesium is a necessary cofactor for numerous enzyme systems and a crucial component of neurochemical transmission and peripheral vasodilatation. Mg levels in the blood may have an impact on cardiac excitability, as well as vascular tone, contractility, and responsiveness [73].

On the other hand, blood zinc level was lower, and iron was higher in preeclamptic women than in the control group, even though this conclusion is uncertain due to the high publication bias in the analysis. Zn is needed for placental formation and regulates maternal blood pressure during pregnancy, and its absence causes fetal development and blood pressure problems. Animal experiments show that zinc deficiency causes aberrant placental morphogenesis and maternal blood pressure [68,74]. On the other hand, iron's role in forming the placenta is not entirely known. Kadyrov et al. [74] revealed that anemia was linked to higher trophoblast apoptosis [75]. Although we did not measure the levels of iron status indicators (such as ferritin), we believe that iron's role in regulating homeostasis is more complicated during pregnancy compared to the general population.

Our study offers some strengths as a meta-analysis of published studies. First, the large number of participants and subgrouped analysis added validity to the results. The results were more logical because we used a random effect model to compute the pooled SMD between serum trace elements level and PE. Third, the study quality was evaluated using the Newcastle-Ottawa scale, and low-quality research (scored 3 and below) would be disregarded. The findings showed that all original papers included were frequently of high quality. The normal reduction in blood trace element levels may occur during pregnancy, so we picked healthy pregnant women as the controls in the original studies we included in our meta-analysis.

However, we also had limitations. Different study designs, clinical techniques, and a biochemical methodology may be the reason for the inconsistencies between various studies. Further research is needed to confirm the relation between serum trace element levels and the disease severity of PE.

CONCLUSION

According to this study, the mean blood levels of Calcium and Magnesium were consistently lower in preeclamptic women compared to normal pregnant women leading to our hypothesis that they might play a role in preeclampsia pathogenesis. Thus, Calcium and Magnesium trace elements supplementation for women before/during pregnancy might help avoid preeclampsia. On the other hand, blood zinc level was lower, and Fe was higher in preeclamptic women; however, this conclusion is uncertain due to the high publication bias in this analysis. Large-scale research would be required to get concrete data on the roles of Ca, Mg, Zn, and Fe and the risk of preeclampsia pathogenesis.

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CONFLICT OF INTEREST

There is no conflict of interest.

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Table 1. Characteristics of the included study

				CALCIUM				
RACE	**COUNTRY**	**AUTHORS**	**YEAR**	**STUDY DESIGN**	**METHOD**	**AGE SUBJECTS**	**GESTATIONAL AGE**	**NOS SCORE**
Africa	Sudan	Abdellah, Ayman et al. [11]	2014	Cross-sectional	Spectrophotometer	24.4-34.6	>20 weeks	8
Africa	Ghana	Anto, Enoch Odame et al [12]	2014	Case-control	Spectrophotometer	21-32.1	26.8-38.9	6
Africa	Nepal	Chaudhary, RK et al. [13]	2018	Cross-sectional	Spectrophotometer	18+	>20	7
Africa	Ghana	Darkwa, Ebenezer Owusu et al [14]	2017	Cross-sectional	Spectrophotometer	25.5-36.5	>30	8
Africa	Addis Ababa	Gebreyohannes, Rahel D et al [15]	2021	Case-control	Spectrophotometer	19-35	>24	7
Africa	Nigeria	Ikechukwu Ikaraoha et al [16]	2012	Cross-sectional	Spectrophotometer	20-35	24-36	5
Africa	Nigeria	Okoror Collins et al. [17]	2020	Cross-sectional	Spectrophotometer	18-35	28-40	7
Africa	Sudan	Sidahmed, Mohanned AE et al [18]	2017	Case-control	Spectrophotometer	19-40	3rd trimester	7
Africa	Ghana	Yeboah, FA et al. [19]	2017	Case-control	Spectrophotometer	23.7-36.7	>20	9
Asia	Egypt	Abdel-Hamid, Mostafa A et al [20]	2019	Case-control	Spectrophotometer	18-37	>20	5
Asia	Dhaka	Ahsan, Touhida et al. [21]	2013	Cross-sectional	Spectrophotometer	19.2-31.5	31.75-38.9	8
Asia	Dhaka	Akhter, A et al [22]	2016	Cross-sectional	Spectrophotometer	23.1-30.5	33.5-40.6	9
Asia	India	Anandpara, Gaurang K et al [23]	2019	Case-control	Spectrophotometer	18-35	28-32	8
Asia	India	Chauhan, Ms Manasvuni et al [24]	2021	Case-control	Spectrophotometer	25.5-36.5	24-38	7
Asia	Uttar Pradesh	Das, Biswajit et al [25]	2016	Cross-sectional	Spectrophotometer	20-35	3trimester	8
Asia	Nepal	Dhungana, Arun et al [26]	2017	Case-control	Spectrophotometer	19.1-26.7	30-40	8
Asia	Karaj, Iran	Hamedanian Laaya et al [27]	2019	Case-control	Spectrophotometer	21.7-30	2-3 trimester	7
Asia	India	Kant, Shashi et al [28]	2019	Cross-sectional	Spectrophotometer	34-40	27-35	5
Asia	Seoul, Korea	Kim, Jihye et al [29]	2012	Case-control	Spectrophotometer	27.5-36.7	31.1-40.2	7
Asia	Chennai	Kokilavani, M et al [30]	2015	Case-control	Spectrophotometer	25.6-38.5	29.6-37.3	8
Asia	Miraj, India	Moholkar, AP et al [31]	2014	Case-control	Spectrophotometer	25.6-38.5	>20	9
Asia	India	Ponnudhali, Manamalli et al [32]	2011	Cross-sectional	Spectrophotometer	20-35	3 trimester	7
Asia	Rajasthan	Poonia, Laxmi et al [33]	2021	Cross-sectional	Spectrophotometer	18-35	>20	6
Asia	India	Rani, Balla Sudha et al [34]	2014	Cross-sectional	Spectrophotometer	22.4-34.45	2 trimester	7

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CALCIUM

RACE	COUNTRY	AUTHORS	YEAR	STUDY DESIGN	METHOD	AGE SUBJECTS	GESTATIONAL AGE	NOS SCORE
Asia	India	Sahay, Sujata, et al [35]	2018	Cross-sectional	Spectrophotometer	20-40	>20	8
Asia	India	Saurabh, Kumar et al [36]	2015	Cross-sectional	Spectrophotometer	15-47	24-40	7
Asia	Jaipur	Sethi S et al [37]	2021	Cross-sectional	Spectrophotometer	21-33	32.8-42	7
Asia	India	Sirajwala, Habibunnisha B et al [38]	2013	Cross-sectional	Spectrophotometer	18-37	>20	9
Asia	India	Sirohiwal, Daya et al [39]	2019	Cross-sectional	Spectrophotometer	20-40	Three trimester	8
Asia	Iran	Tabandeh, Afsaneh et al [4]	2018	Cross-sectional	Spectrophotometer	22.4-34.45	>20	8
Asia	India	Vechalapu, Amulya et al [40]	2020	Cross-sectional	Spectrophotometer	15-35	29.8-40.3	8
Asia	Bandung	Winarno, Gatot N Adhipurnawan et al [41]	2021	Cross-sectional	Spectrophotometer	20-40	>20	9

MAGNESIUM

RACE	COUNTRY	AUTHOR	YEAR	STUDY DESIGN	METHOD	AGE SUBJECTS	GESTATIONAL AGE	NOS
Africa	Sudan	Abdellah, Ayman et al [11]	2014	Cross-sectional	Spectrophotometer	24.4-34.6	>20	9
Africa	Ghana	Anto, Enoch Odame et al [12]	2014	Case-control	Spectrophotometer	34-40	27-35	7
Africa	Nigeria	Atiba, AS et al [42]	2019	Case-control	Spectrophotometer	25-30	19-21	7
Africa	Nepal	Chaudhary, RK et al [13]	2018	Cross-sectional	Spectrophotometer	21-32.1	26.8-38.9	8
Africa	Ghana	Darkwa, Ebenezer Owusu et al [14]	2017	Cross-sectional	Spectrophotometer	25.5-36.5	>30	7
Africa	Nigeria	Ikhile et al [43]	2018	Cross-sectional	Spectrophotometer	21-30	>28	7
Africa	Ghana	Seini, Mohammed et al [44]	2013	Cohort	Spectrophotometer	22.5-34.9	2 trimester	8
Africa	Sudan	Sidahmed, Mohanned AE et al [18]	2017	Case-control	Spectrophotometer	19-40	3 trimester	8
Africa	Ghana	Yeboah, FA et al [19]	2017	Case-control	Spectrophotometer	26.6-35.6	2 trimester	8
Asia	Egypt	Abdel-Hamid, Mostafa A et al [20]	2019	Case-control	Spectrophotometer	18-35	28-40	5
Asia	Dhaka	Ahsan, Touhida et al [21]	2013	Cross-sectional	Spectrophotometer	19.2-31.5	31.75-38.9	8
Asia	Uttar Pradesh	Das, Biswajit et al [45]	2014	Cross-sectional	Spectrophotometer	22-37	24-38	9
Asia	Nepal	Dhungana, Arun et al [26]	2017	Case-control	Spectrophotometer	20-40	>20	8
Asia	Thailand	Kreepala, Chatchai et al [46]	2018	Cohort	Spectrophotometer	20.5-38.5	25.1-36.	5

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MAGNESIUM								
RACE	**COUNTRY**	**AUTHOR**	**YEAR**	**STUDY DESIGN**	**METHOD**	**AGE SUBJECTS**	**GESTATIONAL AGE**	**NOS**
Asia	Miraj, India	Moholkar, AP et al [31]	2014	Case-control	Spectrophotometer	18+	>20	5
Asia	India	Rani, Balla Sudha et al [34]	2014	Cross-sectional	Spectrophotometer	15-47	>20	7
Asia	India	Reddy, Hymavathi K et al [47]	2019	Cohort	Spectrophotometer	19.5-28.3	>20	8
Asia	India	Sahay, Sujata et al [35]	2018	Cross-sectional	Spectrophotometer	15-35	29.8-40.3	8
Asia	Jaipur	Sethi S et al [37]	2021	Cross-sectional	Spectrophotometer	18-32	24-36	9
Asia	Iran	Tavana, Zohreh et al [48]	2013	Cross-sectional	Spectrophotometer	22.7-32.9	30.2-37.8	9
Asia	India	Vechalapu, Amulya et al [40]	2020	Cross-sectional	Spectrophotometer	19-35	>24	8
Asia	Bandung	Winarno, Gatot N Adhipurnawan et al [41]	2021	Cross-sectional	Spectrophotometer	15-47	24-40	5
Europe	Serbia	Cabarkapa Velibor et al [49]	2018	Cohort	Spectrophotometer	22.8-36.7	32.2-40.5	7
Europe	SP, Brazil	Rocha Vivianne et al [50]	2014	Case-control	Spectrophotometer	18-32	26.8-35	9

COPPER								
RACE	**COUNTRY**	**AUTHOR**	**YEAR**	**STUDY DESIGN**	**METHOD**	**AGE SUBJECT**	**GESTATIONAL AGE**	**NOS SCORE**
Asia	Dhaka	Ahsan, Touhida et al [21]	2013	Cross-sectional	Spectrophotometer	20-35	3 trimester	7
Asia	Mymensingh	Baral, Nilima et al [51]	2019	Case-control	Spectrophotometer	19.3-26.5	2-3 trimester	9
Asia	Istanbul	Gul Ayse Zehra et al [52]	2022	Case-control	Spectrophotometer	15-35	3 trimester	7
Asia	Babylon, Iraq	Mudher, Haydar et al [53]	2015	Case-control	Spectrophotometer	20-40	32-38.6	9
Asia	Dhaka	Muna, FZ et al [54]	2015	Cross-sectional	Spectrophotometer	20-40	36.5-37.4	8
Asia	India	Ponnudhali, Manamalli et al [32]	2011	Cross-sectional	Spectrophotometer	23.1-30.5	32-34	8
Asia	Gorgan, Iran	Rafeeinia, Arash et al [55]	2014	Case-control	Spectrophotometer	21-33	31.75-38.9	9
Asia	Iraq	Salih, Lina A et al [56]	2016	Case-control	Spectrophotometer	19-35	27.5-35.1	3
Asia	China	Xu, Huan Ying et al [57]	2020	Cohort	Spectrophotometer	18-35	12-27(+6)	9

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ZINC

RACE	COUNTRY	AUTHOR	YEAR	STUDY DESIGN	METODE	AGE SUBJECT	GESTATIONAL AGE	NOS SCORE
Asia	Dhaka	Ahsan, Touhida et al [21]	2013	Cross-sectional	Atomic absorption spectrometry	22.6-31.7	27.5-35.1	7
Asia	Amman, Jordan	Al-Sakarneh Nawal A., et al [58]	2021	Cross-sectional	Atomic absorption spectrometry	21-35	23-38	8
Asia	Istanbul	Gul Ayse Zehra et al [52]	2022	Case-control	Atomic absorption spectrometry	21.9-37	32-38.6	9
Asia	Seoul, Korea	Kim, Jihye et al [29]	2012	Case-control	Atomic absorption spectrometry	20-35	3 trimester	5
Asia	Babylon, Iraq	Mudher, Haydar et al [53]	2015	Case-control	Atomic absorption spectrometry	27.5-36.7	31.1-40.2	9
Asia	India	Ponnudhali, Manamalli et al [32]	2011	Cross-sectional	Atomic absorption spectrometry	26.3-28.3	36.5-37.4	8
Asia	Gorgan, Iran	Rafeeinia, Arash et al [55]	2014	Case-control	Atomic absorption spectrometry	19.2-31.5	31.75-38.9	5

IRON

RACE	COUNTRY	AUTHOR	YEAR	STUDY DESIGN	METODE	AGE SUBJECT	GESTATIONAL AGE	NOS SCORE
North America	Mexico	Gutierrez-Aguirre et al [59]	2016	Cohort	Atomic absorption spectrometry	21-29.1	33.5-40.6	9
Asia	Dhaka	Ahsan, Touhida et al [21]	2013	Cross-sectional	Atomic absorption spectrometry	18.2-32.9	>20	7
Asia	Dhaka	Ghosh, Lipika et al [60]	2017	Case-control	Atomic absorption spectrometry	19.2-31.5	24-36	7
Asia	Seoul, Korea	Kim, Jihye et al [29]	2012	Case-control	Atomic absorption spectrometry	15-35	>20	8
Asia	Bangalore	Maitra, Sujata et al [61]	2019	Case-control	Atomic absorption spectrometry	26.3-28.3	>20	9
Asia	India	Masti, Shakuntala et al [62]	2014	Case-control	Atomic absorption spectrometry	20-35	29.8-40.3	9
Asia	Babylon, Iraq	Mudher, Haydar et al. [53]	2015	Case-control	Atomic absorption spectrometry	15-35	>24	8

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Table 2. Summary SMD for Trace Elements and the Subgroups

Subgroup			Participants	Studies	SMD	95% CI	Test of SMD		Heterogeneity	
							Z	p for Z	I^2 (%)	P for I^2
Trace Elements		Ca	4746	32	-1.66	-2.05 to -1.28	8.48	<0.00001	97	<0.00001
		Mg	3359	24	-1.28	-1.37 to -1.20	4.99	<0.00001	98	<0.00001
		Cu	2847	9	-0.72	-1.79 to 0.34	1.33	0.18	98	<0.00001
		Zn	598	7	-2.4	-4.11 to -0.7	2.76	0.006	98	<0.00001
		Fe	561	8	1.71	0.21 to 3.21	2.23	0.03	98	<0.00001
Geographical Location	Ca	Asia	3309	23	-1.3	-1.65 to -0.95	7.26	<0.00001	95	<0.00001
		Africa	1437	9	-2.81	-3.91 to -1.71	5.01	<0.00001	98	<0.00001
	Mg	Asia	1383	13	-1.23	-1.95 to -0.51	3.35	0.0008	97	<0.00001
		Africa	1537	9	-2.35	-3.40 to -1.30	4.37	0.0001	98	<0.00001
		Europe	439	2	-1.31	-1.58 to -1.04	9.48	<0.00001	97	<0.00001

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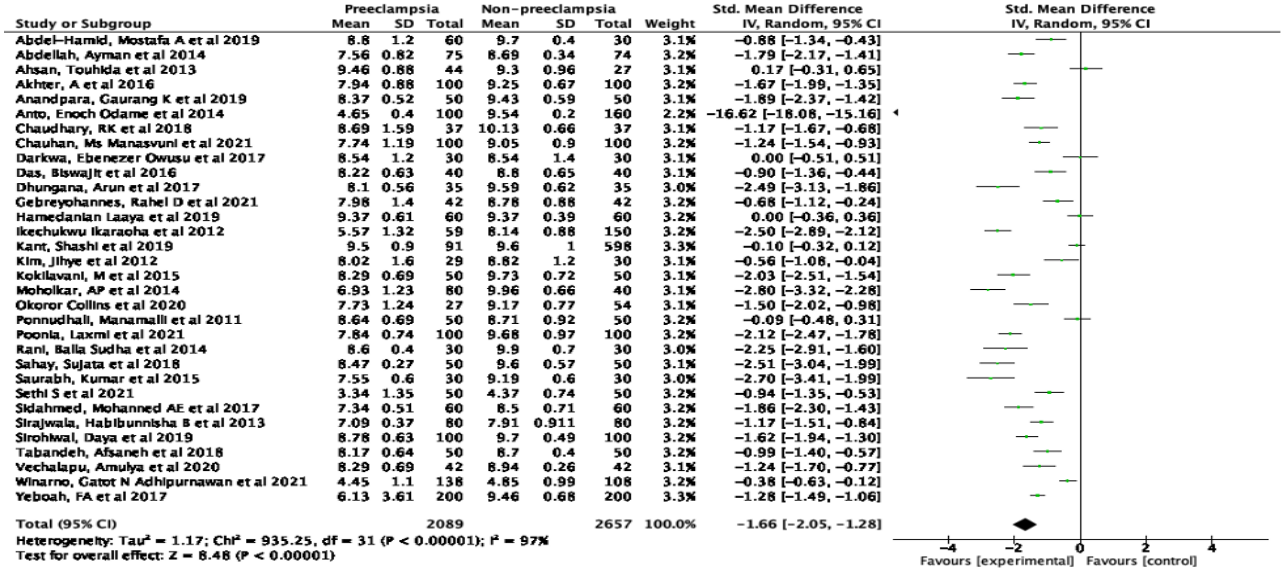


Fig. 2. Forest Plot Pooled SMD for Serum Calcium and Preeclampsia

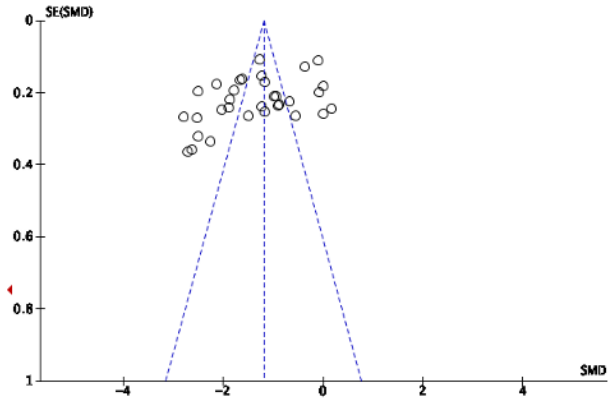


Fig. 3. Funnel Plot Serum Calcium and Preeclampsia

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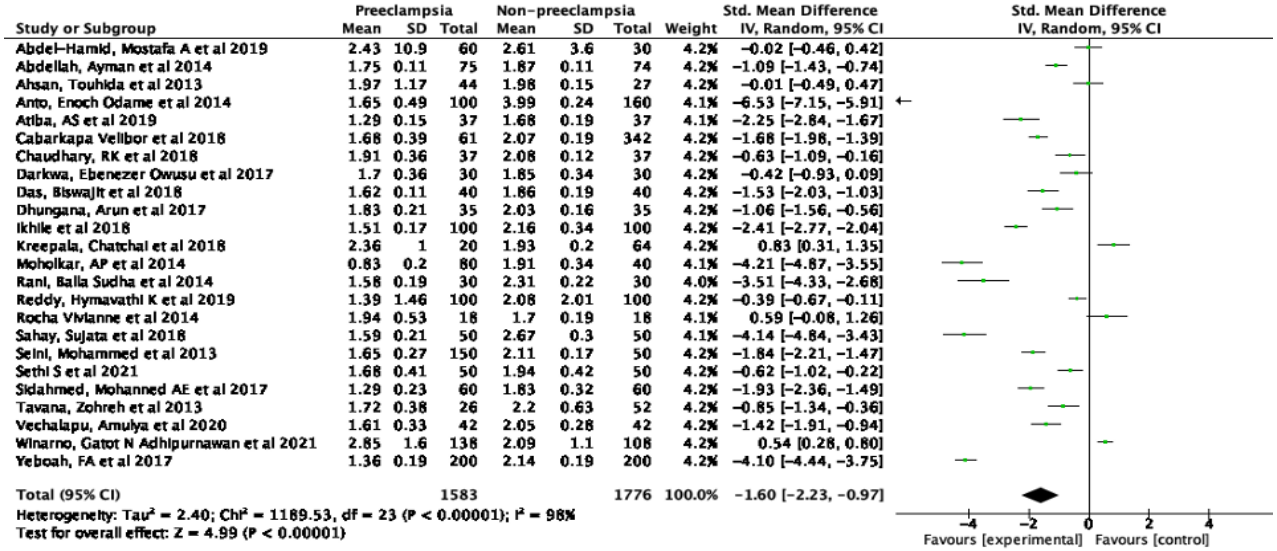


Fig. 4. Forest Plot Pooled SMD for Serum Magnesium and Preeclampsia

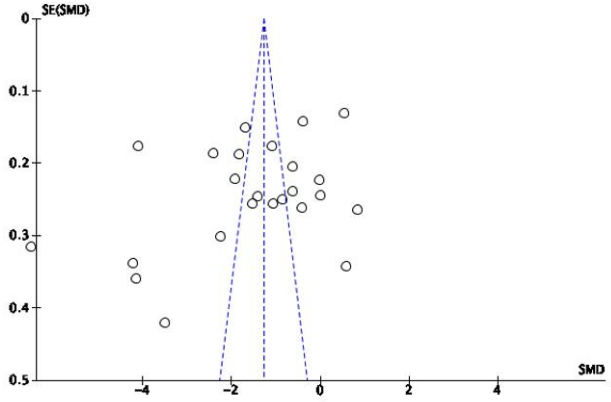


Fig. 5. Funnel Plot Serum Magnesium and Preeclampsia

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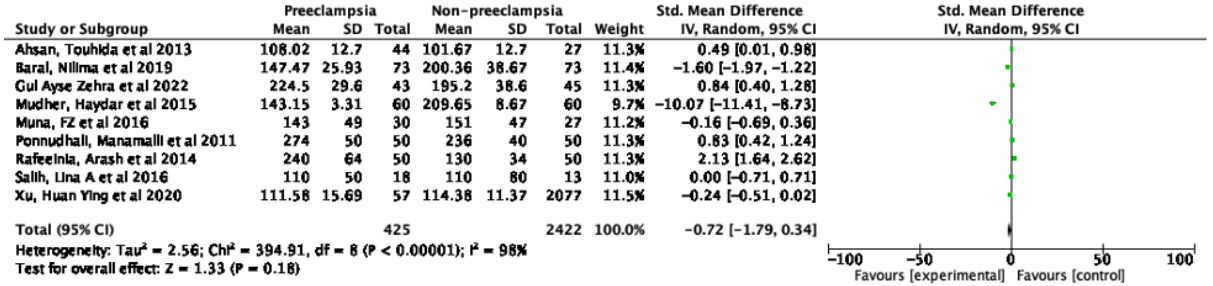


Fig. 6. Forest Plot Pooled SMD for Serum Copper and Preeclampsia

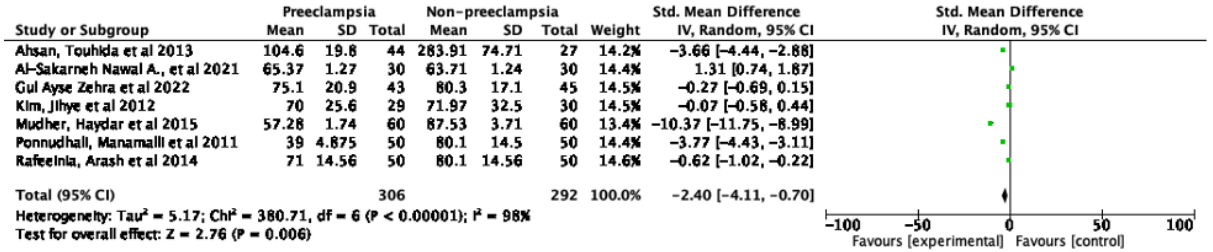


Fig.7. Forest Plot Pooled SMD for Serum Zinc and Preeclampsia

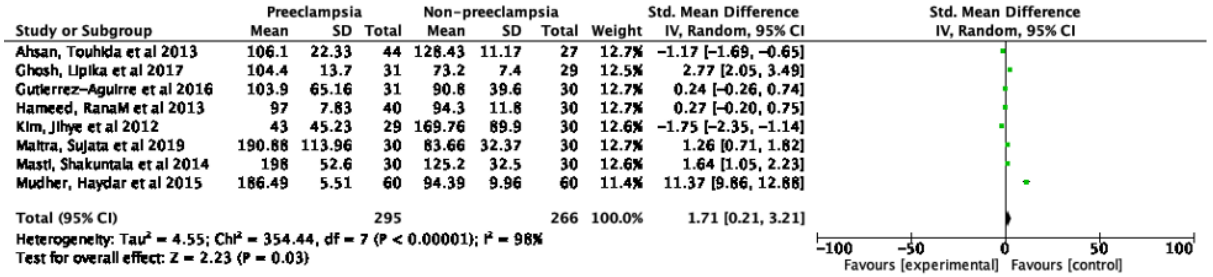


Fig. 8. Forest Plot Pooled SMD for Serum Iron and Preeclampsia

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