**Supplementary Table 1. Characteristics of included studies**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Included studies  (Author + year) | Country | Study type | Age of preeclampsia | | Age of control | | Zinc in PE (Mean±SD) | Zinc in control (Mean±SD) | Unit | Measure method |
| N | (Mean±SD) | N | (Mean±SD) |
| Adam  2001[1] | Turkey | CC | 20 | 29±8 | 20 | 27±6.8 | 31.3±4.7 | 34.1±4.4 | ug/dL | FAAS |
| Ahsan  2013[2] | Bangladesh | CS | 44 | 26.05±5.41 | 27 | 24.11±4.93 | 0.016±0.002 | 0.015±0.002 | mmol/L | AAS |
| Akhtar  2011[3] | Bangladesh | CS | 60 | 25.11±5.66 | 30 | 25.20±4.85 | 902.5±157.15 | 1153.33±67.09 | ugm/L | FAAS |
| Akinloye 2010[4] | South Africa | CS | 49 | NG | 40 | NG | 8.6±1.4 | 9.4±0.8 | umol/L | FAAS |
| Al-Jameil 2014[5] | Saudi Arabia | CC | 40 | 31.55±6.14 | 40 | 31.20±5.84 | 0.67±0.59 | 1.30±0.83 | mg/L | ICP-OES |
| Al-Sakarneh  2021[6] | Jordan | CC | 30 | 28.3±0.8 | 30 | 28.0±0.9 | 63.71±1.24 | 65.37±1.27 | ug/dL | AAS |
| Al-Shalah 2015[7] | Iraq | CC | 60 | 27.72±0.66\* | 60 | 26.85±0.53\* | 57.28±1.74\* | 87.54±3.71\* | ug/dL | FGAAS |
| Atamer  2005[8] | Turkey | CS | 32 | 27.00±3.89 | 28 | 25.85±3.36 | 0.79±0.18 | 1.09±0.20 | mg/L | AAS |
| Bai  2013[9] | China | CC | 41+36 | 28.3±7.6 | 56 | 27.6±7.2 | 7.51±0.56/  6.39±0.33 | 8.96±0.63 | umol/L | NG |
| Bakacak 2015[10] | Turkey | CC | 38 | 29.2±3.56 | 40 | 28.7±3.82 | 81.24±12.06 | 108.45±0.63 | ug/dL | FAAS |
| Borella  1990[11] | Italy | CC | 24 | NG | 35 | NG | 10.49±2.28 | 9.60±2.29 | umol/L | AAS |
| Brito  2013[12] | Brazil | CC | 20+24 | 27.00±6.59 | 50 | 24.13±6.43 | 50.0±9.4/  38.8±8.2 | 48.3±8.3 | ug/dL | FAAS |
| Chababa  2016[13] | Zambia | CS | 41 | NG | 57 | NG | 89.17±47.19 | 76.20±35.23 | mg/dL | AAS |
| Desouky  2020[14] | Egypt | CC | 25 | 22.6±6.7 | 25 | 26.2±5.0 | 60.8±12.8 | 95.7±10.4 | mg/dL | NG |
| El-Moselhy  2010[15] | Egypt | CC | 100 | NG | 100 | NG | 60.81±9.74 | 95.70±12.41 | ug/dL | AAS |
| Elmugabil 2016[16] | Sudan | CC | 50 | 28.6±6.4 | 50 | 28.6±6.6 | 108.0±29.7 | 102.0±30.5 | ug/dL | AAS |
| Enebe  2020[17] | Nigeria | CS | 24+57 | 29.53±5.38 | 81 | 29.31±5.22 | 0.30±0.18/  0.45±0.44 | 0.54±0.80 | mg/L | AAS |
| Farzin  2012[18] | Iran | CC | 60 | 27.43±3.91 | 60 | 26.66±3.72 | 76.49±17.62 | 100.61±20.12 | ug/dL | FAAS |
| Feng  2013[19] | China | CC | 30 | 28.63±6.38 | 30 | 28.73±5.28 | 0.86±0.23 | 0.98±0.21 | ug/mL | AAS |
| Fenzl  2013[20] | Croatia | PC | 30 | 31.2 | 37 | 30.8 | 9.23±1.43 | 8.85±1.43 | umol/L | FAAS |
| Gan  2019[21] | China | CC | 33 | NG | 23 | NG | 10.30±2.98 | 13.44±2.33 | umol/L | AAS |
| Gao  2020[22] | China | CC | 427 | NG | 427 | NG | 6.33±1.75 | 6.49±1.84 | mg/L | ICP-MS |
| Gul  2022[23] | Turkey | CC | 43 | 30.2±6.8 | 45 | 27.2±5.3 | 75.1±20.9 | 80.3±17.7 | ug/dL | Fully automatic photometric method |
| Guo  2013[24] | China | CC | 26+20 | NG | 40 | NG | 61.06±6.24/  56.09±5.86 | 68.77±9.33 | umol/L | FAAS |
| Gupta  2014[25] | India | CC | 47+18 | NG | 75 | NG | 10.46±2.05/  9.28±1.63 | 10.63±1.82 | umol/L | AAS |
| Harma  2005[26] | Turkey | CC | 24 | 26.7±2.6 | 44 | 27.2±2.7 | 15.53±4.92 | 11.93±3.11 | ug/g | AAS |
| Hassan  2014[27] | Sudan | CC | 122 | 29.6±8.0 | 79 | 25.8±6.1 | 49.4±17.0 | 90.3±16.8 | ug/dL | AAS |
| Ikaraoha  2016[28] | Nigeria | CC | 59 | NG | 150 | NG | 45.8±9.7 | 68.2±10.1 | ug/dL | AAS |
| Illhan  2002[29] | Turkey | CC | 21 | NG | 30 | NG | 82.94±28.93 | 125.19±24.23 | ug/dL | AAS |
| Jain  2010[30] | India | CC | 25+25 | 23.04±3.76/  22.96±3.81 | 50 | 23.92±3.42 | 12.72±1.7/  12.04±1.4 | 15.64±2.40 | umol/L | AAS |
| Jamal  2017[31] | Pakistan | CS | 40 | 25.76±0.73 | 40 | 25.46±0.85 | 2.94±0.45 | 5.11±0.21 | mg/dL | FAAS |
| Ji  2010[32] | China | CC | 17+20 | 29.19 | 80 | 28.92 | 68.45±13.8/  66.55±13.5 | 66.45±12.45 | mmol/L | NG |
| Kanagal 2014[33] | India | CC | 60 | 27.45±4.33 | 60 | 25.87±3.11 | 8.84±0.87 | 14.87±0.89 | umol/L | AAS |
| Keshavarz 2017[34] | Iran | CC | 100 | 28.83±5.94 | 100 | 28.36±3.26 | 0.69±0.21 | 0.87±0.30 | mg/L | FAAS |
| Kolusari  2008[35] | Turkey | CC | 47 | 27.91±5.21 | 48 | 27.92±4.25 | 1.06±0.44 | 1.27±0.41 | ug/dL | AAS |
| Lewandowska 2019[36] | Poland | PC | 121 | 35.1±4.2 | 363 | 35.1±4.0 | 615.40±83.60 | 614.6±93.75 | ug/L | ICP-MS |
| Li  2009[37] | China | CC | 36+26 | 27.11±2.90 | 28 | 28.32±3.48 | 7.72±0.53/  6.10±1.40 | 8.91±0.60 | umol/L | Nitro-PAPS |
| Lu  2016[38] | China | CC | 60 | 29.55±2.20 | 30 | 29.60±2.00 | 6.94±1.13 | 8.93±0.54 | umol/L | AAS |
| Maduray 2017[39] | South Africa | CC | 43 | 25±5 | 23 | 24±5 | 18.03±30.28 | 2.13±3.01 | mg/L | ICP-OES |
| McKeating 2021[40] | Australia | NC | 44 | 31.55±3.8 | 193 | 32.24±3.91 | 526.93±111.59 | 510.15±175.70 | ug/L | ICP-MS |
| Memon  2017[41] | Pakistan | CC | 40 | NG | 40 | NG | 0.71±0.04 | 0.88±0.02 | mg/L | AAS |
| Mistry  2015[42] | UK / NZ /  Australia | NCC | 244 | 28 (23, 32)\*\*\* | 472 | 29 (23, 32)\*\*\* | 579.6 [521.1, 638.6]  \*\*\* | 575.7 [515.6, 641.7]  \*\*\* | ug/L | ICP-MS |
| Onyegbule 2016[43] | Nigeria | CC | 54 | 27±7.02 | 48 | 29±5.35 | 12.26±1.83 | 8.27±0.60 | umol/L | AAS |
| Pulei  2018[44] | Kenya | CC | 54 | NG | 54 | NG | 9.9±3.7 | 10.7±3.5 | umol/L | NG |
| Rafeeinia 2014[45] | Iran | CC | 50 | 26.50±3.90 | 50 | 27.10±4.60 | 0.71±0.26 | 0.73±0.33 | mg/L | AAS |
| Rathore 2011[46] | India | CC | 14 | NG | 47 | NG | 49.2±17.8 | 57.5±21.6 | ug/dL | AAS |
| Samar  2020[47] | China | CC | 50 | 29.34±4.35 | 52 | 26.44±4.02 | 85.43±12.07 | 91.79±9.02 | umol/L | Chemical light |
| Sarwar 2013[48] | Bangladesh | CC | 50 | 25.46±0.85\* | 58 | 25.76±0.73\* | 0.77±0.05\* | 0.98±0.03\* | mg/dL | FAAS |
| Ugwuja 2010[49] | Nigeria | CC | 40 | 29.45±3.70 | 40 | 27.55±4.23 | 9.97±9.74 | 10.87±10.28 | umol/L | AAS |
| Yang  2007[50] | China | CC | 47 | 28.75±2.64 | 30 | 26.83±2.59 | 0.76±0.14/  0.68±0.18 | 0.77±0.16 | ug/mL | FAAS |
| Yusrawati  2017[51] | Indonesia | CC | 70 | NG | 70 | NG | 4.80±2.62 | 5.50±3.53 | mg/L | NG |

NC: Nested cohort; NCC: Nested case-control; ICP-MS: Inductively coupled plasma mass spectrometry; ICP-OES: Inductively coupled plasma optical emission spectrometer; NG: Information not given in the article

\*Mean ± SEM (standard error of mean); \*\*Median range (Maximum-minimum); \*\*\*Median (Inter-quartile); #Median±SEM (Minimum, Maximum); +A commercially available procedure for copper measurement

For those studies with sub-group of mild preeclampsia and severe preeclampsia, the mild usually comes first, followed with data of severe preeclampsia, and they were divided with the symbol ‘/’.

**Supplementary Table 2.1. Quality assessment (Modified NOS) for cross-sectional studies**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Included studies | Selection | | | | Comparability | | Outcome | | Score |
| ① | ② | ③ | ④ | ⑤ | ⑥ | | ⑦ |
| Ahsan 2013[2] | ★ | ★ | ★ | ★★ | ★ | ★ | | ★ | 8 |
| Akhtar 2011[3] | ★ | ★ |  | ★ | ★ | ★ | | ★ | 6 |
| Akinloye 2010[4] | ★ |  |  | ★ | ★ | ★ | | ★ | 5 |
| Atamer 2005[8] | ★ | ★ | ★ | ★ | ★ | ★ | | ★ | 7 |
| Chababa 2016[13] | ★ | ★ |  | ★ | ★ | ★ | | ★ | 6 |
| Enebe 2020[17] | ★ | ★ | ★ | ★ | ★ | ★ | | ★ | 7 |
| Jamal 2017[31] |  | ★ | ★ | ★ |  | ★ | | ★ | 5 |

NOS: Newcastle-Ottawa Scale; NA: not applicable

Selection: ① Representativeness of the sample; ② Sample size; ③ Non-repondents; ④ Ascertainment of exposure (risk factors, maximum 2 stars);

Comparability (maximum 2 stars): ⑤ Comparability of outcomes based on the design or analysis;

Outcome (maximum 3 stars): ⑥ Assessment of outcome (maximum 2 stars); ⑦ Statistical test[52]

**Supplementary Table 2.2 Quality assessment (NOS) for cohort studies**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Included studies | Selection | | | | Comparability | Outcome | | | Score |
| ① | ② | ③ | ④ | ⑤ | ⑥ | ⑦ | ⑧ |
| Fenzl 2013[20] | ★ | ★ | ★ | ★ | ★★ | ★ | ★ | ★ | 9 |
| Lewandowska 2019[36] | ★ | ★ | ★ | ★ | ★★ | ★ | ★ | ★ | 9 |
| McKeating 2021[40] | ★ | ★ | ★ | ★ | ★★ | ★ | ★ | ★ | 9 |

Selection: ① Representativeness of the exposed cohort; ② Selection of the non-exposed cohort; ③ Ascertainment of exposure; ④ Demonstration that outcome of interest was not present at the start of study;

Comparability: ⑤ Comparability of cohorts based on the design or analysis;

Outcome: ⑥ Assessment of outcome; ⑦ Was follow-up long enough for outcomes to occur; ⑧ Adequacy of follow up of cohorts

**Supplementary Table 2.3 Quality assessment (NOS) for case-control studies**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Included studies | Selection | | | | | Comparability | | Exposure | | | | | | **Score** |
| ① | ② | ③ | | ④ | ⑤ | ⑥ | | | | ⑦ | | ⑧ |  |
| Adam 2001[1] | ★ | ★ | ★ | |  | ★ | ★ | | ★ | | | | ★ | **7** |
| Al-Jameil 2014[5] | ★ |  |  | |  | ★★ | ★ | | ★ | | | | ★ | **6** |
| Al-Sakarneh 2021[6] | ★ | ★ | ★ | | ★ | ★★ | ★ | | ★ | | | | ★ | **9** |
| Al-Shalah 2015[7] | ★ | ★ | ★ | | ★ | ★★ | ★ | | ★ | | | | ★ | **9** |
| Bai 2013[9] | ★ | ★ | ★ | | ★ | ★★ | ★ | | ★ | | | | ★ | **9** |
| Bakacak 2015[10] | ★ |  | ★ | | ★ | ★★ | ★ | | ★ | | | | ★ | **8** |
| Borella 1990[11] | ★ |  |  | | ★ | ★★ | ★ | | ★ | | | | ★ | **7** |
| Brito 2013[12] | ★ | ★ | ★ | |  | ★ | ★ | | ★ | | | | ★ | **7** |
| Chababa 2018[13] | ★ |  | ★ | | ★ | ★★ | ★ | | ★ | | | | ★ | **8** |
| Desouky 2020[14] | ★ | ★ | ★ | |  | ★★ | ★ | | ★ | | | | ★ | **8** |
| El-Moselhy 2010[15] | ★ |  |  | |  | ★★ | ★ | | ★ | | | | ★ | **6** |
| Elmugabil 2016[16] | ★ |  |  | | ★ | ★★ | ★ | | ★ | | | | ★ | **7** |
| Farzin 2012[18] | ★ |  |  | | ★ | ★★ | ★ | | ★ | | | | ★ | **7** |
| Feng 2013[19] | ★ |  | ★ | | ★ | ★★ | ★ | | ★ | | | | ★ | **8** |
| Gan 2019[21] | ★ | ★ | ★ | | ★ | ★★ | ★ | | ★ | | | | ★ | **9** |
| Gao 2020[22] | ★ | ★ | ★ | |  | ★★ | ★ | | ★ | | | | ★ | **8** |
| Gul 2022[23] | ★ |  |  | | ★ | ★★ | ★ | | ★ | | | | ★ | **7** |
| Guo 2013[24] | ★ |  |  | | ★ | ★★ | ★ | | ★ | | | | ★ | **7** |
| Gupta 2014[25] | ★ |  |  | | ★ | ★★ | ★ | | ★ | | | | ★ | **7** |
| Hama 2005[26] | ★ |  |  | |  | ★★ | ★ | | ★ | | | | ★ | **6** |
| Hassan 2014[27] | ★ |  | ★ | | ★ | ★ | ★ | | ★ | | | | ★ | **7** |
| Ikaraoha 2016[28] | ★ |  | ★ | |  | ★ | ★ | | ★ | | | |  | **5** |
| Illhan 2002[29] | ★ |  | ★ | | ★ | ★★ | ★ | | ★ | | | | ★ | **8** |
| Jain 2010[30] | ★ |  | ★ | |  | ★★ | ★ | | ★ | | | | ★ | **7** |
| Ji 2010[32] | ★ | ★ | ★ | | ★ | ★★ | ★ | | ★ | | | | ★ | **9** |
| Kanagal 2014[33] | ★ |  |  | |  |  | ★ | | ★ | | | | ★ | **4** |
| Keshavarz 2017[34] | ★ | ★ |  | | ★ | ★ | ★ | | ★ | | | | ★ | **7** |
| Kolusari 2008[35] | ★ | ★ |  | |  | ★★ | ★ | | ★ | | | | ★ | **7** |
| Li 2009[37] | ★ |  |  | | ★ | ★★ | ★ | | ★ | | | | ★ | **7** |
| Lu 2016[38] | ★ |  | ★ | |  | ★★ | ★ | | ★ | | | | ★ | **7** |
| Maduray 2017[39] | ★ | ★ |  | |  | ★ | ★ | | ★ | | | | ★ | **6** |
| Memon 2017[41] | ★ |  | ★ | | ★ | ★★ | ★ | | ★ | | | | ★ | **8** |
| Mistry 2015[42] | ★ | ★ | ★ | | ★ | ★★ | ★ | | ★ | | | | ★ | **9** |
| Onyegbule 2016[43] | ★ |  | ★ | | ★ | ★ | ★ | | ★ | | | | ★ | **7** |
| Pulei 2018[44] | ★ | ★ |  | | ★ | ★ | ★ | | ★ | | | | ★ | **7** |
| Rafeeinia 2014[45] | ★ |  |  | |  | ★ | ★ | | ★ | | | | ★ | **5** |
| Rathore 2011[46] | ★ |  |  | |  |  | ★ | | ★ | | | | ★ | **4** |
| Samar 2020[47] |  |  |  | |  | ★★ | ★ | | ★ | | | | ★ | **5** |
| Sarwar 2013[48] | ★ | ★ | ★ | | ★ | ★ | ★ | | ★ | | | | ★ | **8** |
| Ugwuja 2010[49] | ★ |  | | ★ |  | ★ | | ★ | |  | | ★ | | **5** |
| Yang 2007[50] | ★ |  |  | | ★ | ★★ | | ★ | ★ | | | | ★ | **7** |
| Yusrawati 2017[51] | ★ | ★ | |  | ★ | ★ | | ★ | | ★ | | ★ | | **6** |

Selection: ① Is the case definition adequate; ② Representative of the cases; ③ Selection of controls; ④ Definition of controls

Comparability: ⑤ Comparability of cases and controls based on the design or analysis

Exposure: ⑥ Ascertainment of exposure; ⑦ Same method of ascertainment for cases and controls; ⑧ Non-response rate

**Supplementary Table 3 Sensitivity analysis of included studies**

|  |  |  |
| --- | --- | --- |
| Study removed | Estimates after removing the study (95% CI) | I2 (%) |
| Adam 2001[1] | -1.0064 [-1.3043, -0.7086] | 96.7% |
| Ahsan 2013[2] | -1.0285 [-1.3255, -0.7314] | 96.6% |
| Akhtar 2011[3] | -0.9812 [-1.2772, -0.6852] | 96.6% |
| Akinloye 2010[4] | -1.0057 [-1.3049, -0.7065] | 96.7% |
| Al-Jameil 2014[5] | -1.0017 [-1.3005, -0.7029] | 96.7% |
| Al-Sakarneh 2021[6] | -0.9926 [-1.2901, -0.6951] | 96.7% |
| Al-Shalah 2015[7] | -0.9918 [-1.2899, -0.6938] | 96.6% |
| Atamer 2005[8] | -0.9874 [-1.2844, -0.6905] | 96.7% |
| Bai 2013[9] | -0.9592 [-1.2492, -0.6692] | 96.5% |
| Bakacak 2015[10] | -0.9550 [-1.2467, -0.6632] | 96.5% |
| Borella 1990[11] | -1.0261 [-1.3234, -0.7288] | 96.7% |
| Brito 2013[12] | -1.0100 [-1.3095, -0.7105] | 96.7% |
| Chababa 2016[13] | -1.0256 [-1.3235, -0.7277] | 96.6% |
| Desouky 2020[14] | -0.9621 [-1.2561, -0.6682] | 96.6% |
| El-Moselhy 2010[15] | -0.9508 [-1.2348, -0.6668] | 96.3% |
| Elmugabil 2016[16] | -1.0234 [-1.3218, -0.7250] | 96.7% |
| Enebe 2020[17] | -1.0162 [-1.3173, -0.7151] | 96.7% |
| Farzin 2012[18] | -0.9934 [-1.2918, -0.6950] | 96.7% |
| Feng 2013[19] | -1.0082 [-1.3067, -0.7096] | 96.7% |
| Fenzl 2013[20] | -1.0240 [-1.3218, -0.7263] | 96.7% |
| Gan 2019[21] | -0.9961 [-1.2938, -0.6984] | 96.7% |
| Gao 2020[22] | -1.0227 [-1.3370, -0.7085] | 96.6% |
| Gul 2022[23] | -1.0141 [-1.3133, -0.7148] | 96.7% |
| Guo 2013[24] | -0.9941 [-1.2922, -0.6961] | 96.7% |
| Gupta 2014[25] | -1.0042 [-1.3049, -0.7035] | 96.7% |
| Harma 2005[26] | -1.0363 [-1.3318, -0.7408] | 96.6% |
| Hassan 2014[27] | -0.9671 [-1.2570, -0.6772] | 96.4% |
| Ikaraoha 2016[28] | -0.9713 [-1.2631, -0.6796] | 96.5% |
| Illhan 2002[29] | -0.9872 [-1.2840, -0.6903] | 96.7% |
| Jain 2010[30] | -0.9862 [-1.2831, -0.6894] | 96.6% |
| Jamal 2017[31] | -0.9111 [-1.1973, -0.6249] | 96.4% |
| Ji 2010[32] | -1.0210 [-1.3199, -0.7222] | 96.7% |
| Kanagal 2014[33] | -0.8932 [-1.1730, -0.6134] | 96.3% |
| Keshavarz 2017[34] | -1.0064 [-1.3086, -0.7043] | 96.7% |
| Kolusari 2008[35] | -1.0096 [-1.3092, -0.7101] | 96.7% |
| Lewandowska 2019[36] | -1.0218 [-1.3260, -0.7176] | 96.6% |
| Li 2009[37] | -0.9849 [-1.2815, -0.6883] | 96.6% |
| Lu 2016[38] | -0.9777 [-1.2730, -0.6823] | 96.6% |
| Maduray 2017[39] | -1.0310 [-1.3275, -0.7344] | 96.6% |
| McKeating 2021[40] | -1.0220 [-1.3215, -0.7225] | 96.6% |
| Memon 2017[41] | -0.9209 [-1.2081, -0.6337] | 96.4% |
| Mistry 2015[42] | -1.0235 [-1.3321, -0.7148] | 96.6% |
| Onyegbule 2016[43] | -1.0697 [-1.3535, -0.7858] | 96.3% |
| Pulei 2018[44] | -1.0153 [-1.3150, -0.7156] | 96.7% |
| Rafeeinia 2014[45] | -1.0182 [-1.3175, -0.7190] | 96.7% |
| Rathore 2011[46] | -1.0106 [-1.3086, -0.7126] | 96.7% |
| Samar 2020[47] | -1.0076 [-1.3073, -0.7079] | 96.7% |
| Sarwar 2013[48] | -1.0051 [-1.3048, -0.7054] | 96.7% |
| Ugwuja 2010[49] | -1.0175 [-1.3163, -0.7187] | 96.7% |
| Yang 2007[50] | -1.0120 [-1.3109, -0.7131] | 96.7% |
| Yusrawati 2017[51] | -1.0156 [-1.3161, -0.7150] | 96.7% |
| Pooled estimate | -0.9984 [-1.2923, -0.7045] | 96.6% |

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