The role of selenium in depression: a systematic review and meta-analysis of human observational and interventional studies

Sana Sadat Sajjadi1, Sahar Foshati2, Sajjad Haddadian-Khouzani3 & Mohammad Hossein Rouhani1*

The results of human studies are inconsistent regarding selenium and depressive disorders. Therefore, we aimed to conduct a systematic review and meta-analysis of observational and interventional studies and provided an overview of the role of selenium in depression. Three databases including Medline, Scopus, and Web of Science were searched on June 30, 2020 and updated on April 12, 2021. Also, we searched in electronic databases of WHO Global Index Medicus and ClinicalTrials.gov. No time or language restrictions were used for the search. A random effects model was used to pool effect sizes. In total, 20 studies were included in the systematic review, and 15 studies were included in the meta-analysis. There were no significant differences in serum selenium levels between patients with depression and healthy subjects (WMD: 2.12 mg/L; 95% CI: − 0.11, 4.36; I² = 98.0%, P < 0.001). Also, no significant correlation was found between serum levels of selenium and depression scores (r: − 0.12; 95% CI: − 0.33, 0.08; I² = 73.5%, P = 0.010). Nevertheless, there was a significant negative association between high selenium intake and the risk of postpartum depression (OR: 0.97; 95% CI: 0.95, 0.99; I² = 0.0%, P = 0.507). In addition, selenium supplementation significantly reduced depressive symptoms (WMD: − 0.37; 95% CI: − 0.56, − 0.18; I² = 0.0%, P = 0.959). Taken these results together, selenium seems to have a protective role against postpartum depression and can be considered as a beneficial adjuvant therapy in patients with depression. Further studies are necessary to draw definitive conclusions.

Abbreviations

NOS  The Newcastle–Ottawa Scale
CCRBCT  The Cochrane Collaboration Risk of Bias Tool
SE  Standard errors
SD  Standard deviations
CI  Confidence interval
WMD  Weighted mean difference
OR  Odds ratio
r  Correlation

Depression is identified as a disabling mental illness, which can substantially impair quality of life1,2. According to the report of World Health Organization in 2018, more than 264 million people are affected by depression worldwide3. The rate of depression dramatically increased from 172 to 258 million since 1990 to 2017, showing a 50% increase4. Patients with depression may experience fatigue, sleep disturbance, loss of memory...
and concentration, poor appetite, loss of work motivation, and low self-confidence during their lives.\(^5\)\(^6\). Also, untreated depression can lead to serious social problems and even suicide\(^7\).

It appears that nutrition plays a critical role in mental health\(^8\). For instance, several studies have supported the favorable effects of magnesium, vitamin D, B-vitamins, and omega-3 fatty acids on mood disorders\(^9\). Moreover, recent evidence has revealed the benefits of using trace elements in the prevention and treatment of depression\(^10\).

Among trace elements, selenium may be of great importance in the management of depression due to its antioxidant, anti-inflammatory, immunomodulatory, and neuroprotective properties\(^11\)\(^12\). In addition to depression, selenium deficiency may be associated with many other diseases such as type 2 diabetes mellitus, cardiovascular disease, kidney diseases, infertility, and cognitive decline\(^13\)\(^14\).

The results of observational and interventional studies are inconsistent regarding the role of selenium in depression\(^15\)\(^16\)\(^17\). Several studies reported a significant negative relationship between dietary or serum levels of selenium and the risk of depression\(^15\)\(^17\)\(^18\). In contrast, some studies did not find such a relationship\(^19\)\(^20\). Even, a narrative review generally reported that there is an unclear relationship between selenium and depression\(^21\).

Favorable effects of magnesium, vitamin D, B-vitamins, and omega-3 fatty acids on mood disorders\(^9\). Moreover, recent evidence has revealed the benefits of using trace elements in the prevention and treatment of depression\(^10\).

The retrieved articles were included in the present study if they met the following criteria: (1) had an observational (cross-sectional, case–control, and cohort) or an interventional (randomized controlled trial) design, (2) conducted on humans, (3) investigated the association between dietary or supplemental intake or serum levels of selenium and depression, (4) compared dietary or supplemental intake or serum levels of selenium between patients with depression and healthy controls, and (5) assessed the effect of selenium supplementation or selenium rich diet on depression. The exclusion criteria were: (1) reviews, books, case reports, conference papers, letters to the editor, and animal or in vitro studies, (2) studies which failed to assess selenium, (3) studies which administered selenium in combination with other components, (4) studies which measured nail or hair selenium, and (5) studies reported duplicate data, (6) studies which assessed other outcomes other than depression, (7) protocol study, and (8) studies which failed to assess the association between selenium and depression.

The quality assessment of observational studies was performed using the Newcastle–Ottawa Scale (NOS)\(^26\), and the quality of interventional studies was evaluated using the Cochrane Collaboration Risk of Bias Tool (CCRBT)\(^27\).

To improve normal distribution, correlation coefficients between serum selenium levels and depression scores were converted to z-values using Fisher’s r-to-z transformation. Subsequently, following formula was used to convert back to r-values when effect sizes were calculated: ES (z) = \(\frac{1}{2} \ln \left[\frac{(1 + r)/(1 - r)}{1 + \sqrt{1 - r^2}}\right]\). We converted standard errors (SE) to standard deviations (SD) using the formula SD = SE × \(\sqrt{N}\). To calculate SD from 95% confidence interval, following formula was used: SD = \(\sqrt{N} \times (\text{upper limit} - \text{lower limit})\). A random-effects model was used to calculate pooled effect size to compare serum selenium levels between depressive patients and healthy controls\(^29\). We used the random-effects model because inter-study heterogeneity was high. The random-effects model should be used for pooling heterogeneous studies\(^30\). Similar method was applied to compare depression scores between selenium supplementation and control groups. Since included clinical trials used different tools to assess depression score, pooled effect was calculated via Hedges’ \(g\)\(^31\). Log-transformed odds ratios of depression across different categories of selenium intake were also applied to calculate overall effect sizes. Overall effect sizes were reported as odds ratio (OR), weighted mean difference (WMD) and correlation coefficient (r). I-squared (I\(^2\)) statistic was reported as an indicator of between-study heterogeneity. To detect the potential sources of heterogeneity, a subgroup analysis was applied when a significant between-study heterogeneity was observed. Sensitivity analysis was performed as a complementary analysis to assess robustness of results. Begg’s rank correlation test and Egger’s linear regression test were used to test publication bias. The potential effect of publication bias was assessed using trim-and-fill analysis. All statistical analyses were performed using Stata software (version 11.2, Stata Corporation, College Station, Texas, USA); additionally, analyses were two-tailed, and statistical significance was set at \(P < 0.05\).
Results

Study selection process. Initially, 1794 published articles were identified from the electronic databases (Fig. 1). After removing 495 duplicates, 1299 records were assessed for eligibility, and 1214 studies were excluded based on screening title and abstract (unrelated studies (n = 853), evaluation other outcomes other than depression (n = 37), selenium intake/concentration was not reported (n = 21), animal studies (n = 235), in vitro studies (n = 37), review articles (n = 27) and protocol studies (n = 4). After screening full-text of the records, 65 studies were excluded due to the following reasons: review articles (n = 20), letters to the editor (n = 8), books and case reports (n = 3), selenium was not measured (n = 2), selenium in combination with other components (n = 8), unrelated data (n = 12), nail selenium (n = 1), conference paper (n = 1), other outcomes other than depression (n = 2), hair selenium (n = 1), no full text available (n = 2), did not assess the association between selenium and depression (n = 5).
reports (n = 3), failure to assess selenium (n = 2), administration of selenium in combination with other components (n = 8), unrelated data (n = 12), measurement of nail selenium levels (n = 1), conference papers (n = 1), evaluation other outcomes other than depression (n = 2), measurement of hair selenium levels (n = 1) full text of articles were not available at databases or journal website (n = 2) and the association between selenium and depression was not assessed (n = 5). Finally, 20 studies were included in the systematic review.

**Systematic review.** Characteristics of studies eligible for the systematic review are summarized in Table 1. These studies were published between 2003 and 2020. Among twenty studies, two were conducted in New Zealand, four in Iran, four in the US, three in Spain, three in Argentina, one in Australia, one in Canada, one in the UK, one in Bangladesh, one in Chile, one in Poland, one in Columbia, and one study in.

Malaysia. Four studies were randomized controlled trials, nine studies used a cross-sectional design, four were case-control studies, and design of three studies were prospective cohort. In total, 47,164 participants were enrolled in this systematic review. The age of participants ranged from 18.0 ± 1.2 to 82 years old. Twelve studies included both men and women, one study did not report the gender of participants, and seven studies enrolled women only. Serum selenium concentrations were measured in four cross-sectional studies, two case-controls, and one prospective cohort. Selenium intake levels were used in two case-controls, six cross-sectional studies, and two prospective cohort studies. Only nine studies specified the type of depression including postpartum depression (n = 4), major depressive disorder (n = 3), pregnant depression (n = 1), and postmenopausal depression (n = 1). Serum selenium concentrations between patients with depression and healthy controls were assessed in four studies. The Beck Depression Inventory, Edinburgh Postnatal Depression Scale, and mood thermometer were used to measure dietary/supplementary selenium intake and the risk of depression. All interventional studies used selenium supplements except for one study that assessed the effect of selenium rich diet on depression symptoms. The dose of selenium supplementation was varied from 100 to 200 μg. A beneficial effect of selenium on depressive symptoms was reported in three studies. However, one clinical trial found no significant effect of selenium on depression scores.

**Quality assessment of studies.** The results of the CCRBT showed that all included randomized controlled trials had high quality (Table 2). According to the NOS, all case–control and prospective cohort studies obtained ≥4 stars, i.e., low quality scores (Tables 3, 4). Similarly, the quality of all cross-sectional studies was low except for Ghimire and Li that respectively received good and excellent quality (Table 5).

**Meta-analysis.** From 20 studies included in systematic review, five studies were not selected for meta-analysis. Two studies not included to meta-analysis reported the correlation coefficient between dietary intake of selenium and depression symptoms. We could not pool these two studies because the score of depression was derived from different depression assessment instruments. One study was not included to meta-analysis because it reported median depression score across tertiles of plasma selenium concentration. A reported selenium intake across tertiles of mood thermometer was Since similar report was not found in other studies, we did not include this study to meta-analysis. Another study not selected for meta-analysis reported regression coefficient. Therefore, a quantitative analysis was performed on 15 studies including 45,795 participants. Correlation between serum selenium levels and depression scores was assessed in four studies. The meta-analysis showed no significant correlation between serum levels of selenium and depression scores (r: −0.12, 95% CI: −0.33, 0.08) (Fig. 2). Although a significant between-study heterogeneity was found (I² = 73.5%, P = 0.010), we could not run a subgroup analysis due to the insufficient number of studies. Moreover, there was an evidence of significant publication bias using Egger’s (P = 0.029) and Begg’s (P = 0.042) tests. Notwithstanding, trim-and-fill analysis indicated that no trimming could be performed and the data remained unchanged.

Comparison of serum selenium levels between depressive patients and healthy controls was reported in two studies. As shown in Fig. 3, the pooled results revealed that there were no significant differences in serum selenium concentrations between patients with depression and healthy subjects (WMD: 2.12 mg/L; 95% CI: −0.11, 4.36). There was a significant heterogeneity between studies (I² = 98.0%, P < 0.001). However, we could not run a subgroup analysis because of the insufficient number of studies. Moreover, the result did not show...
| First author (year) | Country | Sample size (male/female) | Age (mean ± SD, median (IQR), year) | Design | Reported data | Type of depression | Depression assessment tool | Results | Adjusted variables |
|---------------------|---------|--------------------------|-----------------------------------|-------|---------------|----------------------|--------------------------|---------|------------------|
| Amini (2019)        | Iran    | 163 (0/163)              | 27.79 ± 6.1                       | Case–control | Risk of depression, Mean of dietary selenium | PPD | EPDS | A more selenium intake was associated with an reduced risk of depression | Energy intake and BMI |
| Banikazemi (2016)   | Iran    | 7172 (2725/4447)        | 48.55 ± 7.4                       | Cross-sectional | Risk of depression | NR | BDI | Selenium intake was negatively associated with the relative risk of a high depression score | Energy intake |
| Conner (2015)       | New Zealand | 978 (357/621)        | 19.6 ± 1.6                        | Cross-sectional | Mean of depression score | NR | CESD | A negative association between serum selenium and risk of depression | Age, gender, ethnicity, BMI, and mean weekly alcohol intake |
| Ekramzadeh (2015)   | Iran    | 150 (17/133)            | 47.23 ± 13.6                      | Cross-sectional | Correlation between serum selenium and depression score, Mean of serum selenium | NR | BDI | No significant association between depression score and serum selenium | Age, sex, marriage, job, and education level |
| Ghimire (2019)      | US      | 7725 (3723/4002)        | 46.4 (32.5–59.7)                  | Cross-sectional | Risk of depression (serum and dietary) | NR | PHQ-9 | An inverse association between dietary selenium and depression, No significant association between serum selenium and depression | |
| Gosney (2008)       | UK      | 59 (NR)                 | 82 (NR)                           | Randomized controlled trial | Correlation between serum selenium and depression score, Effect of dietary selenium supplementation on depression score | NR | MADRS | A significant negative relationship between serum selenium and depression, Significant reduction in depression score in active group | NR |
| Ibarra (2015)       | Spain   | 77 (18/59)              | 50.46 ± 11.6                      | Randomized controlled trial | Correlation between serum selenium and depression score | MDD | HDRS-17 BDI | Active group had a better outcome of depressive symptoms, An inverse association between serum selenium and depression | NR |
| Islam (2018)        | Bangladesh | 495 (192/303)      | 33.29 ± 0.6                       | Case–control | Mean of serum selenium in healthy and depressed subjects | MDD | SCID-5 | MDD patients had lower levels of selenium | NR |
| Jin (2020)          | New Zealand | 87 (0/87)              | 31.5 ± 4.2                        | Cohort | Median of serum selenium | PPD | EPDS | No significant association between plasma selenium values and prevalence of depression | NR |
| Leung (2013)        | Canada  | 475 (0/475)             | 31.4                               | Cohort | Risk of depression | PPD | EPDS | Supplementary selenium intake was negatively associated with the risk of depression | NR |

Continued
| First author (year) | Country | Sample size (male/female) | Age (mean ± SD, median (IQR), year) | Design | Reported data | Type of depression | Depression assessment tool | Results | Adjusted variables |
|---------------------|---------|---------------------------|------------------------------------|--------|--------------|-------------------|--------------------------|--------|-------------------|
| Li (2018)           | US      | 14,834 (7399/7435)        | 24.99                              | Cross-sectional | Risk of depression | NR                  | PHQ-9                    | Total selenium intake was negatively associated with depression | RML, race, educational level, smoking status, family income, work activity, recreational activity, hypertension, diabetes, energy intake, age, and gender |
| Mokhber (2011)      | Iran    | 85 (0/85)                 | 21.61 ± 2.9                        | Randomized controlled trial | Effect of selenium supplementation on depression score | PPD                | EPDS                     | Selenium group had lower mean EPDS score | NR |
| Pasco (2012)        | Australia | 316 (0/316)              | 54.5                               | Nested case-control | Risk of depression | MDD                | SCID-I                   | A low selenium intake was associated with an increased risk of de novo MDD | Age, socioeconomic status, smoking, alcohol use, and physical activity |
| Perez-Cornago (2015)| Spain   | 84 (47/37)                | 49.4 ± 2.7                         | Cross-sectional | Mean of dietary selenium in healthy and depressed subjects | NR                | BDI                      | Intake of more selenium was associated with better mood | Sex, age, and energy intake |
| Samad (2019)        | Pakistan | 96 (13/83)               | 50                                 | Case–control | Mean of serum selenium in healthy and depressed subjects | NR                | HDRS-17                   | Depression was associated with selenium deficiency | NR |
| Sánchez-Villegas (2018) | Spain | 13,983 (5880/8103)      | 38.2 ± 11.9                        | Cohort | Risk of depression | NR                | SCID-I                   | Inadequate selenium intake was related to increased risk of depression | Sex, age, physical activity, energy intake, BMI, special diets, smoking, and prevalence of diseases such as cardiovascular disease, hypertension, and type 2 diabetes |
| Shor-Posner (2003)  | Miami   | 63 (32/31)                | 40.0 ± 6.4                         | Randomized controlled trial | Effect of selenium supplementation on depression score | NR                | BDI                      | No significant change in the prevalence of depression | NR |
| Singh (2017)        | Columbia | 108 (0/108)              | 18.0 ± 1.2                         | Cross-sectional | Correlation between selenium intake and depression score | Pregnant depression | RADS                     | No significant association between selenium intake and depressive symptoms | Energy intake |
| Wieder-Husza (2020) | Poland  | 102 (0/102)              | 56.69 ± 6.0                        | Cross-sectional | Correlation between serum selenium and depression score | Postmenopausal depression | BDI                    | No significant association between depression score and serum selenium | NR |
| Tatt (2019)         | Malaysia | 112 (56/56)              | 71.4 ± 7.0                         | Cross-sectional | Correlation between selenium intake and depression score | NR                | GDS-15                   | No significant association between GDS score and selenium intake, but a negative association between selenium intake and GDS score in males | NR |

Table 1. Overview of the studies included in the systematic review. NR: Not reported, BMI: Body mass index, MDD: Major depressive disorder, PPD: Postpartum depression, EPDS: Edinburgh Postnatal Depression Scale, CESD: Center for Epidemiological Studies–Depression, BDI: Beck Depression Inventory, MADRS: Montgomery-Asberg Depression Rating Scale, HDRS-17: 17-item Hamilton Depression Rating Scale, PHQ-9: 9-item Patient Health Questionnaire, SCID-5: Structured Clinical Interview for DSM-5, SCID-1: Structured Clinical Interview for DSM-IV Axis I Disorders, RADS: Reynolds Adolescent Depression Scale. GDS-15: 15-items Chinese Geriatric Depression Scale.
any evidence of publication bias using Begg’s test (P = 0.31). Egger’s test was not run for this section due to the insufficient number of studies.

Association between selenium intake and the risk of depression was reported in seven studies. The pooled risk of depression in the highest compared with the lowest categories of selenium intake was 0.98 with 95% CI of 0.93 to 1.04. A significantly high heterogeneity was observed between studies (I² = 82.7%, P < 0.001). Therefore, we subgrouped studies based on the type of depression (postpartum or other types of depression) (Fig. 4). There was a significant association between selenium intake and the risk of postpartum depression (OR: 0.97; 95% CI: 0.95, 0.99; I² = 0.0%, P = 0.507). Nevertheless, no significant association was found between selenium intake

### Table 2. Quality assessment of the included randomized controlled trials according to the Cochrane Collaboration Risk of Bias Tool. Symbols: +, low risk of bias; ?, unclear risk of bias; –, high risk of bias.

| First author (year) | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding of participants and personnel (performance bias) | Blinding of outcome assessment (detection bias) | Incomplete outcome data (attrition bias) | Selective reporting (reporting bias) | Other sources of bias | Score |
|---------------------|--------------------------------------------|-----------------------------------------|----------------------------------------------------------|---------------------------------------------|--------------------------------------|-----------------------------------|-------------------|-------|
| Shor-Posner (2003)  | +                                          | +                                       | +                                                        | +                                           | +                                    | +                                | High              |
| Mokhber (2011)      | +                                          | +                                       | ?                                                        | ?                                           | +                                    | +                                | High              |
| Ibarra (2015)       | +                                          | +                                       | ?                                                        | ?                                           | +                                    | +                                | High              |
| Gosney (2008)       | +                                          | +                                       | +                                                        | +                                           | +                                    | +                                | High              |

### Table 3. Quality assessment of the included case–control studies according to the Newcastle–Ottawa Scale.

| First author (year) | Adequate definition of cases | Representativeness of cases | Selection of controls | Definition of controls | Control for important factors or additional factors | Exposure assessment | Same method of ascertainment for cases and controls | Non-response rate | Total quality score |
|---------------------|-------------------------------|-----------------------------|-----------------------|------------------------|------------------------------------------------------|---------------------|-------------------------------------------------|------------------|---------------------|
| Amini (2019)        | –                             | –                           | –                     | *                      | –                                                    | –                   | *                                              | –                | 3                   |
| Islam (2018)        | –                             | –                           | *                     | *                      | –                                                    | –                   | –                                              | –                | 4                   |
| Pasco (2012)        | –                             | –                           | *                     | **                     | –                                                    | –                   | –                                              | –                | 4                   |
| Samad (2019)        | –                             | –                           | –                     | –                      | –                                                    | –                   | –                                              | –                | 1                   |

### Table 4. Quality assessment of the included cohort studies according to the Newcastle–Ottawa Scale.

| First author (year) | Representativeness of the exposed cohort | Selection of the non-exposed cohort | Ascertainment of exposure | Outcome not present at start of study | Comparability of cohorts | Assessment of outcome | Follow-up long enough for outcomes to occur | Adequacy of follow-up of cohorts | Total quality score |
|---------------------|-------------------------------------------|-------------------------------------|---------------------------|--------------------------------------|-------------------------|-----------------------|---------------------------------------------|-----------------------------|---------------------|
| Jin (2020)          | –                                         | *                                   | –                         | –                                    | –                       | –                     | –                                           | –                           | 2                   |
| Leung (2013)        | –                                         | –                                   | –                         | –                                    | –                       | –                     | –                                           | –                           | 1                   |
| Sánchez-Villesgas (2018) | –                                     | *                                   | –                         | –                                    | –                       | –                     | –                                           | –                           | 4                   |

### Table 5. Quality assessment of the included cross-sectional studies according to the Newcastle–Ottawa Scale.

| First author (year) | Representativeness of the sample | Sample size | Non-respondents | Ascertainment of the exposure | Comparability of outcome groups | Assessment of outcome | Statistical test | Total score |
|---------------------|----------------------------------|-------------|-----------------|-------------------------------|---------------------------------|-----------------------|-----------------|-------------|
| Banikazemi (2016)   | –                                | –           | –               | –                             | *                               | –                     | –               | 1           |
| Conner (2015)       | –                                | –           | –               | *                             | *                               | –                     | –               | 4           |
| Ekramzadeh (2015)   | –                                | –           | –               | *                             | –                               | –                     | –               | 3           |
| Ghimire (2019)      | *                                | –           | –               | –                             | *                               | –                     | –               | 6           |
| Li (2018)           | *                                | *           | –               | –                             | *                               | –                     | –               | 7           |
| Perez-Cornago (2015) | –                             | –           | –               | *                             | –                               | –                     | –               | 3           |
| Singh (2017)        | –                                | –           | *               | –                             | –                               | –                     | –               | 4           |
| Wieder-Huszla (2020) | –                             | –           | –               | –                             | –                               | –                     | –               | 3           |
| Tatt (2019)         | *                                | –           | *               | –                             | –                               | –                     | –               | 5           |
and the risk of other types of depression (OR: 1.06; 95% CI: 0.75, 1.50; \(I^2 = 85.6\%), \(P < 0.001\)). Between-subgroup heterogeneity was also high for the type of depression (\(P = 0.012\)). Moreover, we did not find any evidence of publication bias using Egger’s (\(P = 0.65\)) and Begg’s (\(P = 0.80\)) tests.

The Effect of selenium supplementation on depression scores was examined in three studies. The effect of supplementation with selenium on depression scores is shown in Fig. 5. The meta-analysis indicated a significant reduction in depression symptoms following selenium supplementation compared with placebo (WMD: −0.37; 95% CI: −0.56, −0.18). There was no significant heterogeneity between studies (\(P = 0.00\), \(P = 0.959\)). Moreover, no evidence of publication bias was found using Egger’s (\(P = 0.11\)) and Begg’s (\(P = 0.12\)) tests.

Sensitivity analysis. The sequential exclusion of each study from the pooled analysis did not significantly change the overall effect sizes except for the correlation between serum selenium concentrations and depression scores. This was significantly altered by excluding the study of Ekramzadeh et al. (\(r = −0.20\); 95% CI: −0.381, −0.031). In addition, the sequential removal of each study from the pooled analysis did not eliminate the heterogeneity except for the association between selenium intake and the relative risk of depression.

Discussion
This meta-analysis revealed that there was no significant correlation between serum selenium levels and depression scores. In addition, no significant differences were observed between depressive and healthy subjects in serum selenium concentrations. In contrast, a significant inverse association was found between selenium intake and the risk of postpartum depression. Moreover, the meta-analysis of randomized controlled trials indicated a significant reduction in depression symptoms after selenium supplementation compared with placebo. To the
best of our knowledge, the present study is the first systematic review and meta-analysis of human observational and interventional studies that comprehensively investigated the role of selenium in depressive disorders. Prior to this study, three systematic reviews suggested that nutrients such as selenium may be protective against postpartum depression. Nevertheless, these studies only focused on perinatal depression, not other types of depression. Moreover, they did not run a meta-analysis. The findings of this meta-analysis did not show any significant correlation between serum selenium concentrations and depression scores. In contrast, one study reported that there was a significant direct association between high dietary selenium intake and mood improvement. According to the previous studies, serum selenium levels could not estimate the absolute intake of selenium. In fact, some factors including demographic variables and health status may influence serum selenium concentrations. Among the studies included in the present meta-analysis, confounding variables were adjusted in only one study. Moreover, it seems that brain function is impaired by long-term (not short-term) exposure to low serum selenium levels. In spite of this
fact, the included studies reported no data regarding the duration of selenium deficiency. These reasons may explain the non-significant association between serum selenium and depression symptoms in our meta-analysis. Nevertheless, it is noteworthy that removal of the study by Ekramzadeh et al. significantly changed this result and brought about a significant negative correlation between serum concentrations of selenium and depression scores. Ekramzadeh et al. investigated the relationship of serum selenium with depression in hemodialysis subjects. They measured serum levels of selenium before the beginning of the hemodialysis session and adjusted multiple confounding factors, unlike other three included studies.

In this study, no significant association was observed between selenium intake and the risk of depression. The included observational studies estimated selenium intake from foods as well as nutritional supplements. Therefore, it is possible that their results were confounded by the bioavailability of dietary or supplementary selenium. Cumulative evidence has proposed that selenium bioavailability is affected by the chemical form of selenium (organic or inorganic). Organic selenium is more bioavailable than inorganic selenium and also retains in tissues more. Similarly, the effectiveness of inorganic supplements of selenium has been reported to be less than that of organic supplements. Moreover, components such as heavy metals, fiber, lipids, dietary sulfur, and oxalate can have antagonistic effects on the bioavailability of dietary selenium. Furthermore, selenium methionine and selenium cysteine were decreased during cooking processes. Unfortunately, the included studies did not report any data on the bioaccessibility and bioavailability of selenium in diet or supplements. Future studies need to be focused on these issues.

The subgroup analysis revealed that high selenium intake was significantly associated with low risk of postpartum depression. Due to the placental transfer of selenium to the fetus, maternal serum selenium levels are reduced during pregnancy, especially in the 3rd trimester. In addition, selenium is secreted in maternal breast milk as a component of selenoproteins. These processes increase the daily selenium requirement of pregnant and lactating women, which may result in selenium deficiency if not compensated properly. It should be noted that supplementary selenium is more effective than dietary selenium in the improvement of low serum selenium levels. In this meta-analysis, all studies conducted on postpartum depression considered supplementary, but not dietary, intake of selenium. This could contribute to the observed significant association between selenium intake and the risk of postpartum depression.

Interestingly, the present meta-analysis indicated that selenium supplementation significantly decreased depressive symptoms. Several mechanisms can explain this beneficial effect of selenium on depression. Selenium is known as a key regulatory factor of inflammatory and oxidative responses. Selenium deficiency can disrupt the function of multiple antioxidant enzymes such as glutathione peroxidase and thioredoxin reductases, which protect cells against oxidative damage. Furthermore, inflammation is regarded as a part of depression pathogenesis. Therefore, anti-inflammatory properties of selenium may help to improve depressive symptoms. It is also possible that selenium affects depression symptoms through the modulation of neurotransmitter turnover as well as regulation of thyroid function.

Several techniques have been suggested to determine serum concentration of selenium including atomic absorption spectrometry, molecular, atomic fluorescence spectrometry, inductively coupled plasma-mass spectrometry (ICP-MS) and graphite furnace atomic absorption spectrometry, flame atomic absorption, electrothermal atomic absorption spectrometry. Atomic fluorescence spectrometry has higher sensitivity and is simpler than atomic absorption spectrometry. However, it has some detection limits. Flame graphite atomic absorption spectrometry is a selective, sensitive and easy method, however it is a single element technique. ICP-MS is higher sensitivity than atomic spectrometry. It has multi-element capability, good stability and detects qualitative and quantitative trace element. However, this method is relatively expensive. As a result, the different methodologies used to measure selenium in serum may be considered as one of the sources of heterogeneity. The method used to measure serum concentration of selenium in included studies are reported in Supplementary Table 1. Unfortunately, we could not evaluate the effect of this factor on the study findings. It has been proposed that serum concentration of selenium may be affected by sex and age. The association between serum selenium level and gender is not clear. Some previous investigations indicated that there was no significant difference in serum selenium between males and females. However, several studies reported serum concentration of selenium was related to gender. Some studies reported that serum selenium concentration was higher in men compared with women. In contrast, one study revealed that women had higher serum selenium in comparison with men. It is possible that some factors including differences in sexual hormones, smoking and dietary habits play a role in relationship between gender and serum selenium level. Also, the findings of studies regarding the effect of age on serum selenium concentration are inconsistent. According to the previous studies, no significant association between serum selenium and age was found. However, this finding was not approved by some studies. It seems that changes in body selenium distribution, dietary habits and hormonal status probably affect selenium concentration through different ages. For example, plasma estrogen is positively related to serum selenium. Therefore, change of estrogen status throughout the life cycle can influence serum selenium in women. Moreover, a significant reduction in serum selenium has been reported in elderly individuals. Accumulation of inflammatory factors, change in physiology conditions, inadequate intake of selenium-rich sources and inefficient absorption of dietary selenium are contributed in the relationship between the declined serum selenium level and aging.

This study has several limitations. First, there were high levels of heterogeneity in all analyses except for the effect of selenium supplementation on depression scores. Second, due to the insufficient number of studies, we could not run subgroup analyses for all outcomes except for selenium intake and the relative risk of depression.
Third, potential confounding factors were not adjusted in some of the included studies, which might affect the findings.

Strengths of the present study should also be considered. First, this study is the first meta-analysis that investigated the role of selenium in depressive disorders. Second, we conducted a comprehensive search using several databases to identify eligible studies. Third, we included both interventional and observational studies in this systematic review and meta-analysis to perform a comprehensive assessment regarding selenium and depression.

Conclusion
In conclusion, the findings of this systematic review and meta-analysis suggest that high selenium intake may have a protective role against postpartum depression. In addition, our findings support that supplementation with selenium can be effective in reducing depressive symptoms. Nevertheless, further studies are needed to draw definitive conclusions.

Data availability
The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Received: 4 September 2021; Accepted: 6 January 2022
Published online: 20 January 2022

References
1. Depression WHO. Other Common Mental Disorders: Global Health Estimates 1–24 (World Heal Organ, 2017).
2. Vilagut, G., Forero, C. G., Barbaglia, G. & Alonso, J. Screening for depression in the general population with the center for epidemiologic studies depression (CES-D): A systematic review with meta-analysis.PLoS ONE 11(5), e0155431. https://doi.org/10.1371/journal.pone.0155431 (2016).
3. James, S. L. et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: A systematic analysis for the Global Burden of Disease Study 2017. Lancet 392(10159), 1789–1858 (2018).
4. Liu, Q. et al. Changes in the global burden of depression from 1990 to 2017: Findings from the Global Burden of Disease study. J. Psychiatry. Res. 126, 134–140 (2020).
5. Maj, M. Validity and clinical utility of the current operational characterization of major depression. Int. Rev. Psychiatry. 24(6), 530–537 (2012).
6. Gawlik, S. et al. Subclinical depressive symptoms during pregnancy and birth outcome—A pilot study in a healthy German sample. Arch. Womens Ment. Health 16(2), 93–100 (2013).
7. organiWH. Depression. Fact Sheet N 369 (World Health Organization, 2013).
8. Kaplan, B. J., Field, C. J., Crawford, S. G. & Simpson, J. S. A. Vitamins, minerals, and mood. Psychol. Bull. 133(5), 747–760 (2007).
9. Skarupski, K. A. et al. Longitudinal association of vitamin B-6, folate, and vitamin B-12 with depressive symptoms among older adults over time. Am. J. Clin. Nutr. 92(2), 330–335 (2010).
10. Jiang, J. et al. Dietary intake of human essential elements from a Total Diet Study in Shenzhen, Guangdong Province, China. J. Food Compos. Anal. 39, 1–7 (2015).
11. Rayman, M. P. The importance of selenium to human health. Lancet 356(9225), 233–241 (2000).
12. Rayman, M. P. Selenium and human health. Lancet 379(9822), 1256–1268 (2012).
13. Wang, X., Yang, T., Wei, J., Lei, G. & Zeng, C. Association between serum selenium level and type 2 diabetes mellitus: A non-linear dose–response meta-analysis of observational studies. Nutr. J. 15(1), 48 (2015).
14. Shahar, A. et al. Plasma selenium is positively related to performance in neurological tasks assessing coordination and motor speed. Mov. Disord. 25(12), 1909–1915 (2010).
15. Conner, T. S., Richardson, A. C. & Miller, J. C. Optimal serum selenium concentrations are associated with lower depressive symptoms and negative mood among young adults. J. Nutr. 145(1), 59–65 (2015).
16. Amini, S. et al. The relationship between dietary intakes during pregnancy and incidence of postpartum depression: A case–control study. Nutr. Food Sci. 50, 751–764 (2019).
17. Sánchez-Villegas, A. et al. Micronutrient intake adequacy and depression risk in the SUN cohort study. Eur. J. Nutr. 57(7), 2409–2419 (2018).
18. Ekramzadeh, M., Mazloom, Z. & Sagheb, M. Association of depression with selenium deficiency and nutritional markers in the patients with end-stage renal disease on hemodialysis. J. Ren. Nutr. 25(4), 1305–1317 (2020).
19. Wieder-Haasla, S. et al. The severity of depressive and anxiety symptoms in postmenopausal women depending on their magnesium, zinc, selenium and copper levels. J. Elem. 25(4), 104–108 (2011).
20. Goosney, M. A., Hammond, M. F., Shenkin, A. & Allsup, S. Effect of micronutrient supplementation on mood in nursing home residents. Gerontology 54(3), 292–299 (2008).
21. Shor-Pesner, G. et al. Psychological burden in the era of HAART: Impact of selenium therapy. Int. J. Psychiatry Med. 33(1), 55–69 (2003).
22. Wang, J., Um, P., Dickerman, B. A. & Liu, J. Zinc, magnesium, selenium and depression and implications. Nutrients 10, 1–19 (2018).
23. Group, K. O. et al. Meta-analysis of observational studies in epidemiology: A proposal for reporting. JAMA 283(15), 2008–2012. https://doi.org/10.1001/jama.283.15.2008 (2000).
24. Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G. & Group, P. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med. 6(7), e1000097 (2009).
25. Wells, G. A., et al. The Newcastle–Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. 2009. http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm.
26. Higgins, J. P. Cochrane handbook for systematic reviews of interventions. Version 5.1.0 (updated March 2011) (2011). The Cochrane Collaboration. www.cochrane-handbook.org.
27. Jerng, R. et al. Research on Data Conversion Method in Meta Analysis (Southern Medical University, 2014).
28. DerSimonian, R. & Laird, N. Meta-analysis in clinical trials. Control Clin. Trials 7(3), 177–188 (1986).
29. DerSimonian, R. & Kacker, R. Random-effects model for meta-analysis of clinical trials: An update. Contemp. Clin. Trials 28(2), 105–114 (2007).
30. Hedges, L. & Olin, I. Statistical Methods for Meta-Analysis (Academic Press, 2014).
32. Choong, H., Adzram, S., Ibrahim, Z. & Norazman, C. Nutritional status in relation to depressive symptoms among Chinese elderly in Malaysia. Malays. J. Med. Health Sci. 15, 53–60 (2019).
33. Leung, B. M. Y. et al. Prenatal micronutrient supplementation and postpartum depressive symptoms in a pregnancy cohort. BMC Pregnancy Childbirth 13, 2 (2013).
34. Iin, Y., Coad, J., Pond, R., Kim, N. & Brough, L. Selenium intake and status of postpartum women and postnatal depression during the first year after childbirth in New Zealand—Mother and Infant Nutrition Investigation (MINI) Study. J. Trace Elem. Med. Biol. 61, 126503 (2020).
35. Perez-Cornago, A., Zuleta, M. A. & Martinez, J. A. Association between mood and diet quality in subjects with metabolic syndrome participating in a behavioural weight-loss programme: A cross-sectional assessment. Nutr. Neurosci. 18(3), 137–144 (2015).
36. Ibara, O. et al. The Mediterranean diet and micronutrient levels in depressive patients. Nutr. Hosp. 31(3), 1171–1175 (2015).
37. Li, Z., Wang, W., Xin, X., Song, X. & Zhang, D. Association of total zinc, iron, copper and selenium intakes with depression in the US adults. J. Affect. Disord. 1(228), 68–74 (2018).
38. Ghimire, S., Baral, B. K., Deng, D., Sy, F. S. & Rodriguez, R. Is selenium intake associated with the presence of depressive symptoms among US adults? Findings from National Health and Nutrition Examination Survey (NHANES) 2011–2014. Nutrition 1(62), 169–176 (2019).
39. Samad, N., Yasmin, F. & Manzoor, N. Biomarkers in drug free subjects with depression: Correlation with tryptophan. Psychiatry Investig. 16(12), 948–953 (2019).
40. Islam, M. R. et al. Alterations of serum macro-minerals and trace elements are associated with major depressive disorder: A case–control study. BMC Psychiatry 18(1), 1–7 (2018).
41. Banikazemi, Z., Mirzaei, H., Mokhber, N. & Mobarhan, M. G. Selenium intake is related to beck’s depression score.
42. Singh, A.
43. Pasco, J. A.
44. Sparling, T. M., Henschke, N., Nesbitt, R. C. & Gabrysch, S. The role of diet and nutritional supplementation in perinatal depression: A systematic review. Matern. Child Nutr. 13(1), e12235 (2017).
45. Farooq, S., Singh, S. P., Burke, D., Naeem, F. & Ayub, M. Pharmacological interventions for prevention of depression in high risk conditions: Systematic review and meta-analysis. J. Affect. Disord. 269, 58–69 (2020).
46. Xiao-hua, Z. & Zhi-hua, Z. Risk factors for postpartum depression: An evidence–based systematic review of systematic reviews and meta-analyses. Asian J. Psychiatr. 53, 102353. https://doi.org/10.1016/j.ajp.2020.102353 (2020).
47. Finlay, J. W. & Penland, J. G. Adequacy or deprivation of dietary selenium in healthy men: Clinical and psychological findings. J. Trace Elem. Exp. Med. 11(1), 11–27 (1998).
48. Duffield, A. J. & Thomson, C. D. A comparison of methods of assessment of dietary selenium intakes in Otago, New Zealand. Br. J. Nutr. 82(2), 131–138 (1999).
49. Gao, S. et al. Selenium level and depressive symptoms in a rural elderly Chinese cohort. BMC Psychiatry 12, 72 (2012).
50. Thomson, C. D. Assessment of requirements for selenium and adequacy of selenium status: A review. Eur. J. Clin. Nutr. 58(3), 391–402 (2004).
51. Schrauzer, G. N. & Surai, P. F. Selenium in human and animal nutrition: Resolved and unresolved issues. A partly historical treatise in commemoration of the fiftieth anniversary of the discovery of the biological essentiality of selenium, dedicated to the memory of Klaus Schwarz (1914–1978) on the occasion of the thirtieth anniversary of his death. Crit. Rev. Biotechnol. 29(1), 2–9 (2009).
52. Hamilton, S. J. Review of selenium toxicity in the aquatic food chain. Sci. Total Environ. 326(1–3), 1–31 (2004).
53. Robinson, M. F. & Thomson, C. D. The role of selenium in the diet. Nutr. Abstr. Rev. 40, 3–26 (1983).
54. Khanam, A. & Platel, K. Bioaccessibility of selenium, selenomethionine and selenocysteine from foods and influence of heat processing on the same. Food Chem. 194, 1293–1299 (2016).
55. Bedwal, R. S. & Bahuguna, A. Zinc, copper and selenium in reproduction. Experientia 50(7), 626–640 (1994).
56. Combs, G. F., Clark, L. C. & Turnbull, B. W. An analysis of cancer prevention by selenium. Eur. J. Clin. Nutr. 50(7), 58–69 (2000).
57. Mertens, K. et al. Alterations of serum macro-minerals and trace elements are associated with major depressive disorder: A systematic review. Meta-analyses. J. Affect. Disord. 91(1–2), 249–257 (2003).
58. Boss, C. & Fredeen, K. J. Concepts, Instrumentation and Techniques in Atomic Absorption Spectrophotometry 2–12 (Perkin Elmer, 1997).
59. Wilschefski, S. C. & Baxter, M. R. Inductively coupled plasma mass spectrometry: Introduction to analytical aspects. Clin. Biochem. 40(3), 115–133 (2019).
60. Ghayour-Mobarhan, M., Taylor, A., New, S. A., Lamb, D. J. & Ferns, G. A. A. Determinants of serum copper, zinc and selenium in healthy subjects. Ann. Clin. Biochem. 42(5), 364–375 (2005).
75. Lopes, P. A. et al. Trace element status (Se, Cu, Zn) in healthy Portuguese subjects of Lisbon population: A reference study. *Biol. Trace Elem. Res.* **101**(1), 1–17 (2004).
76. Li, N. et al. Selenium level in the environment and the population of Zhoukoudian area, Beijing, China. *Sci. Total Environ.* **381**(1–3), 105–111 (2007).
77. Korunová, V. et al. Serum selenium in adult Czechoslovak (central bohemia) population. *Biol. Trace Elem. Res.* **37**(2–3), 91–99 (1993).
78. Kafi, M. R. & Ganji, V. Sex, age, geographical location, smoking, and alcohol consumption influence serum selenium concentrations in the USA: Third National Health and Nutrition Examination Survey, 1988–1994. *J. Trace Elem. Med. Biol.* **17**(1), 13–18 (2003).
79. Safaralizadeh, R. et al. Serum concentration of selenium in healthy individuals living in Tehran. *Natr. J.* **4**, 1–4 (2005).
80. Letsiou, S. et al. Serum total selenium status in Greek adults and its relation to age. The ATTICA study cohort. *Biol. Trace Elem. Res.* **128**(1), 8–17 (2009).
81. Althman, G. & Neve, J. Reference values for serum selenium in various areas-evaluated according to the TRACY protocol. *J. Trace Elem. Med. Biol.* **10**(2), 77–87. https://doi.org/10.1016/S0946-672X(96)80015-0 (1996).
82. Arnaud, J. et al. Serum selenium determinants in French adults: The SU.VI.M.AX study. *Br. J. Nutr.* **95**(2), 313–320 (2006).
83. Pavão, M. L. et al. Comparison of whole-blood glutathione peroxidase activity, levels of serum selenium, and lipid peroxidation in subjects from the fishing and rural communities of “Rabo de Peixe” village, San Miguel Island, The Azores’ archipelago, Portugal. *Biol. Trace Elem. Res.* **92**(1), 27–40 (2003).
84. Wgosowicz, W. & Zachara, B. A. Selenium concentrations in the blood and urine of a healthy polish sub-population. *Clin. Chem. Lab. Med.* **25**(7), 409–412 (1987).
85. Lee, O., Moon, J. & Chung, Y. The relationship between serum selenium levels and lipid profiles in adult women. *J. Nutr. Sci. Vitaminol. (Tokyo)* **49**(6), 397–404 (2003).
86. Letsiou, S. et al. Gender-specific distribution of selenium to serum selenoproteins: Associations with total selenium levels, age, smoking, body mass index, and physical activity. *BioFactors* **40**(5), 524–535 (2014).
87. Adolf, L. Recommended dietary allowances. *Clin. Pediatr. (Philia.)* **3**(122), 630–632 (1964).
88. Behne, D. & Hofer-Bosse, T. Effects of a low selenium status on the distribution and retention of selenium in the rat. *J. Nutr.** **114**(7), 1289–1296 (1984).
89. Smith, A. M., Chang, M. P. H. & Medeiros, L. C. Generational differences in selenium status of women. *Clin. Pediatr. (Phila.)* **39**(7), 157–165 (2000).
90. Lloyd, B., Lloyd, R. S. & Clayton, B. E. Effect of smoking, alcohol, and other factors on the selenium status of a healthy population. *J. Epidemiol. Community Health* **37**(3), 213–217 (1983).
91. Ravaglia, G. et al. Blood micronutrient and thyroid hormone concentrations in the oldest-old. *J. Clin. Endocrinol. Metab.* **85**(6), 2260–2263 (2000).
92. Ekmekcioglu, C. The role of trace elements for the health of elderly individuals. *Nahrung Food.* **45**(5), 309–316 (2001).

Acknowledgements

Food Security Research Center, Isfahan University of Medical Sciences, Isfahan, Iran supported present study.

Author contributions

S.H. and M.H.R. designed the study, M.H.R., S.H. and S.S.S. searched databases. S.S.S. screened the studies and checked inclusion and exclusion criteria. M.H.R. and S.F. analyzed the study. S.S.S. and S.F. wrote the manuscript. M.H.R. revised the manuscript.

Funding

There is no financial arrangement between an author and a company whose product figures prominently in the submitted manuscript. This study was supported by Isfahan University of Medical Sciences [Grant Number 199229].

Competing interests

The authors declare no competing interests.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-022-05078-1.

Correspondence and requests for materials should be addressed to M.H.R.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher’s note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

© The Author(s) 2022