Systematic Review

Lack of sufficient evidence to support a positive role of selenium status in depression: a systematic review

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Context: *Globally, depression affects more than 322 million people. Studies exploring the relationship between diet and depression have revealed the benefits of certain dietary patterns and micronutrients in attenuating the symptoms of this disorder. Among these micronutrients, selenium stands out because of its multifaceted role in the brain.* ***Objective:*** *To assess the impact of selenium intake and status on symptoms of depression.* ***Data Sources:*** *A systematic search was performed in databases, including PubMed, Web of Science, EMBASE, PsycINFO, Scopus, and gray literature (on April 6, 2021, updated on January 28, 2022), without restrictions of date, language, or study type.* ***Data Extraction:*** *Studies of adults (18–60 y of age) with depression or depressive symptoms were included. Data on selenium biomarkers and/or intake were included. The risk of bias was assessed using the Joanna Briggs Institute checklists.* ***Data Analysis:*** *Of the 10 studies included, 2 were cohorts (n = 13 983 and 3735), 3 were cross-sectional (n = 736, 7725, and 200), 1 was case-control (n = 495), and 4 were randomized controlled trials (n = 30, 11, 38, and 63). Several studies have indicated that low selenium intake or concentration may be associated with symptoms of depression. However, this association was inconsistent across the studies included in this systematic review; due to the high heterogeneity, it was not possible to perform meta-analyses. The main contributing factors to the high heterogeneity include the different methodological designs, methods for diagnosing depression, selenium assessment, and clinical conditions.*
Conclusion: *Overall, there is insufficient evidence to support a positive role of selenium status in depression. Studies with more accurate methods and adequate assessment of selenium status are needed to better understand the role of this nutrient in depression.*
Systematic Review Registration*: PROSPERO registration no. CRD42021220683.*

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INTRODUCTION

Depression represents a wide spectrum of symptoms related to changes in mood, interest, and pleasure that lead to difficulties in social, family, educational, and professional life, which sometimes lead to the concomitant occurrence of somatic symptoms and anxiety.[1] Depression is the second most common mental disorder; it affects more than 322 million people globally and is identified as 1 of the 3 main causes of illness in the past 30 years.[2,3]

Data on the treatment costs of depression are scarce, but the estimated costs of mental health policies and programs in the period 2011–2030 are estimated to be US$16.1 trillion.[4] Chisholm et al[5] reported important projections on the annual costs of treating depressive and anxiety disorders. Reports were also issued on lost productivity. Considering the absence of scaled-up treatment in the 36 largest countries in the world, the authors projected more than 12 billion days of lost productivity due to depressive and anxiety disorders each year, with an estimated cost of US$925 billion. Considering the cost distribution in high- and low-income countries, the global expenditure due to these mental health problems is approximately US$1.15 trillion.[5]

Although the etiology of depression remains unclear, there is evidence of the interplay among genetic, biological, and environmental factors in the neurobiological pathways involved in the pathophysiology of this disease.[6] Thus, lifestyle factors seem to play a major role in the onset of mental disorders. In this regard, sedentary behavior, irregular sleeping patterns, tobacco smoking, and poor diet are linked to an increased risk of depression.[7]

A growing body of research exploring the association between diet and depression has revealed the benefits of certain dietary patterns, macronutrients, and micronutrients in the prevention and treatment of depression.[8] Among these micronutrients, selenium has been investigated because of its multifaceted role in the brain.[9,10] Selenium is an essential component of the antioxidant system in the brain. The major reason for this is because of the activities of the selenoproteins glutathione peroxidases (GPx) and thioredoxin reductases. Selenium also regulates mitochondrial biogenesis and calcium channels, and experimental studies have suggested it is associated with the increased synthesis of brain-derived neurotrophic factor, which is essential for neuroplasticity (reviewed by Cardoso et al[10]).

Given the importance of selenium in the central nervous system, it is hypothesized that adequate selenium status is associated with a reduced risk of depression and depressive symptoms. This hypothesis aligns with preclinical studies of animals, results of which suggest that selenium plays an antidepressant role by acting on the dopaminergic and serotonergic systems.[11] Therefore, for this systematic review, we aimed to assess the impact of selenium intake and status on the symptoms of depression in adult individuals.

METHODS

Protocol and registration

The systematic review protocol was registered in the International Prospective Registry of Systematic Reviews registration no: CRD42021220683). The Preferred Reporting Item for Systematic Reviews and Meta-Analyses (PRISMA)[12] guidelines were followed throughout the review.

Information sources and research strategy

The acronym PICOS (population, intervention, comparison, outcomes, and study design) (Table 1) was used to formulate the research question. The search strategy comprised the following terms: ("adult OR adults") OR ("depressive patients") AND ("selenium" OR "selenium compounds") AND ("depression*" OR "depressive symptoms" OR "depressive symptom" OR "symptom depressive" OR "symptoms depressive" OR "emotional depression" OR "depression emotional") OR ("depression" AND "emotional"). The systematic research was performed in the PubMed, Scopus, Web of Science, EMBASE, and PsycINFO databases. In addition, gray literature was searched on Google Scholar (limited to the first 400 records), as recommended by Pizato et al.[13] In the second phase, manual searches were performed in the reference lists of articles included in this systematic review.

The search was carried out on April 6, 2021, updated on January 28, 2022, and there were no date and language restrictions on both dates. All studies meeting the eligibility criteria (Table 1) in the first search and in the updated search were included. As recommended by Greenhalgh and Peacock,[14] systematic-review team experts were consulted to improve the search results. Details on the adapted searches for each of the databases are shown in Table S1 (Supporting Information online). The Rayyan web app[15] was used to identify duplicate articles, and the Mendeley Reference Management Software, version 1.19.8,[16] was used to organize the references.

Table 1 **PICOS criteria for inclusion of studies**

Parameter	Inclusion criteria	Exclusion criteria
Population	Adults aged 18–60 y	Individuals younger than 18 y and older than 60 y Pregnant, postpartum, and menopausal women Animal models or in vitro studies Individuals without a diagnosis of depression Concomitant evaluation of other micronutrients without individual analysis of selenium biomarkers or intake
Intervention or exposure	Interventions based on diet modifications Interventions with selenium supplementation Exposure to dietary patterns assessed by direct weighing of food or dietary records Selenium concentrations and glutathione peroxidase activity assessed in plasma, serum, nails, hair, or erythrocytes	Multinutrient supplementation without individual analysis of selenium
Comparison	Control diets (low selenium diets) Placebo interventions Normal blood and nails selenium biomarkers	Concomitant evaluation of other micronutrients without individual analysis of selenium biomarkers or intake
Outcome	Occurrence of depressive symptoms (depressed mood, low self-esteem, reduced interest or mood, reduced ability to concentrate, fatigue, sleep problems and reduced or loss of appetite) Changes in depression assessment scores Prevalence of depression Risk of developing depression Episodes of major depressive disorders	No reporting of depression analysis tools No reporting of depression in an extractable format
Study design	Observational studies (cohort, case-control, and cross-sectional) Intervention studies (randomized controlled trials and experimental)	Missing and/or unclear data even after requesting information from the authors, letters, reviews, conference abstracts, personal opinion articles, case reports, poster presentations, and news summary

Screening

A 2-phase screening process was conducted by 2 independent reviewers to select the articles. Two reviewers (A.C.S. and A.F.F.P.) excluded the identified duplicate articles before starting the first phase. In the first phase, the 2 reviewers independently screened the titles and abstracts of all identified articles using the Rayyan web app.[15] Articles that did not meet the eligibility criteria were removed. In the second phase, the same 2 reviewers involved in the first phase independently applied the eligibility criteria to the comprehensive reading of the articles. Differences in opinions in the 2 phases were forwarded to a third reviewer (L.C.H.) for consensus. The same screening process was adopted in the search strategy update.

Data extraction

The extraction was carried out independently by 2 authors (A.C.S. and A.F.F.P.) and the collected data were then compared. Disagreements were decided by a third author (L.C.H.) when necessary. Data on the publication (year, authors, country, and type of study), participants (age, sex, health conditions, sample size, and groups), selenium intake (diet and supplement), selenium markers (in plasma: selenium and selenoprotein P; in serum: selenium; in erythrocytes: selenium and GPx activity; and nails), and depression (diagnosis: yes/no, symptoms, assessment tools, and periodicity of the evaluation) were extracted. Type and period of intervention were also extracted for randomized controlled trials (RCTs).

Publication bias

The risk-of-bias assessment of eligible articles also was performed by the same 2 reviewers using the Joanna Briggs Institute tools according to the types of studies (case-control, RCT, cohort, and cross-sectional).[17,18] The information required by the checklist was queried in all the included articles. The answer was "Yes" when the article met the requirement, "No" when it did not, "Unclear" when it was not clear in the article, and "NA" when not applicable. A third author (L.C.H.) was consulted to resolve any potential disagreement.

The categories applied to assess the risk of bias were based on a recent systematic review that also used the Joanna Briggs Institute checklists.[19] The authors classified the articles as having high, moderate, and low

risk of bias when presenting "yes" percentages of up to 49%, between 50% and 69%, and greater than 70%, respectively.[19]

RESULTS

Study selection

The first database query retrieved a total of 950 records, of which the gray literature was the source of 50 records. After excluding duplicates (n = 235), 715 records remained for the screening process. After screening titles and abstracts, 668 records were removed because they did not meet the eligibility criteria. The manual search performed in the reference lists of the articles included in the first phase resulted in the addition of 4 new articles. Moreover, 1 article was included by recommendation of 1 systematic-review team expert. Of these 5 articles, 4 were excluded. In the search update, 92 studies were screened and 8 were assessed for eligibility. Of these 8, only 1 was included in the systematic review. In total, 56 articles were read comprehensively (Figure 1).[12] Of these 56 articles, 46 were removed (Table S2 in the Supporting Information online). Considering the first and the updated searches, 10 studies were included in the systematic review (Figure 1).[12] The article included by recommendation of a systematic-review team expert in the first search was retrieved in the updated search; however, it was considered a duplicate and removed (Table S2).

Study characteristics

The characteristics of the 10 studies included in the present systematic review are shown in Table 2.[20–29] The oldest study dates to 1996,[20] and the most recent was published in 2021.[21] Six observational studies (2 cohort studies,[22,23] 3 cross-sectional studies,[21,24,25] 1 case-control study[26]), and 4 RCTs were included.[20,27–29] These studies were carried out in 5 countries: the United States,[20,23,24,27,29] Brazil,[21] Bangladesh,[26] Sweden,[28] Spain,[22] and Iran.[25] The sample size of these studies ranged from 11[20] to 13 983[22] adults who were either healthy[20–23,25] or were HIV$^+$,[29] had Graves' disease,[28] depression episodes,[21] or major depressive disorder (MDD).[26]

Selenium dietary intake was assessed in 4 observational studies[21,22,24,25] and 2 RCTs.[20,27] Dietary assessment was carried out using 4 different methods: food frequency questionnaire,[22,25] 24-hour recall,[21,24] food diary,[20] and laboratory analysis of selenium content in the diet.[27] Blood was the most common sample across the studies. It was used to determine selenium concentration in plasma,[29] serum,[24,26] and erythrocytes,[20] as well as to measure selenoprotein P concentration[28] and GPx activity.[27] Nails were used for the assessment of selenium concentration in 1 study.[23]

Regarding the outcomes, depression was assessed in 4 studies,[21,22,25,28] and the presence of depressive symptoms was evaluated in 2 studies.[23,24] MDD was investigated in 1 study.[26] Mood was evaluated in 2 studies,[20,27] and psychological burden was examined in 1 study.[29] Depression and depressive symptoms were evaluated using different validated tools: (1) the Profile of Mood States Bipolar Scale (POMS-Bi), which measures mood and how it is created[20,27,29]; (2) the Beck's Depression Inventory, which assesses depression and its symptoms[25,29]; (3) the Hospital Anxiety and Depression Scale, which identifies the presence of depression and anxiety[28]; (4) the *Diagnostic and Statistical Manual of Mental disorders, Fifth Edition* (*DSM-V*), which identifies and defines depression as a common disorder involving almost complete loss of interest[21,22,26]; (5) the symptom questionnaire (from the Rivermead Post-Concussions Symptom Questionnaire), which contains brief and simple items that are sensitive for clinical research, such as scales of depression state, anxiety, anger or hostility, and somatic symptoms[28]; (6) the Center for Epidemiological Studies Depression Scale, which contains 20 items developed to evaluate depressive symptoms[23]; (7) the major depressive episodic module of the mini-international neuropsychiatric interview, Brazilian version, which identifies the main mood disorders of the *DSM-V*[21]; and (8) a validated Patient Health Questionnaire–9, which identifies symptoms of depression.[24] Sánchez-Villegas et al[22] used baseline self-reported information from patients, which was validated in a subsample by the structured clinical interview with *DSM-IV* (Structured Clinical Interview for DSM-5–I), a questionnaire that was standardized in a previous study for the reliability of self-reported information.

Publication bias

A summary of the quality assessment is presented in Figure 2.[20–29] In brief, 9 studies showed a low risk of bias because they satisfied greater than 70% of the tools' evaluation criteria and only the study of Finley et al[27] presented a moderate risk of bias, with 53.9% "Yes" in the checklist for RCTs. No study presented a high risk of bias. The studies by Ghimire et al,[24] Ferreira de Almeida et al,[21] and Shokati et al[25] resulted in 100%, 75.0%, and 75.0% "Yes" answers in the checklist for analytical cross-sectional studies, respectively. The studies by Shor-Posner et al,[29] Hawkes et al,[20] and Calissendorff et al[28] presented 92.3%, 92.3%, and 84.6% "Yes" answers in the checklist for RCTs, respectively.

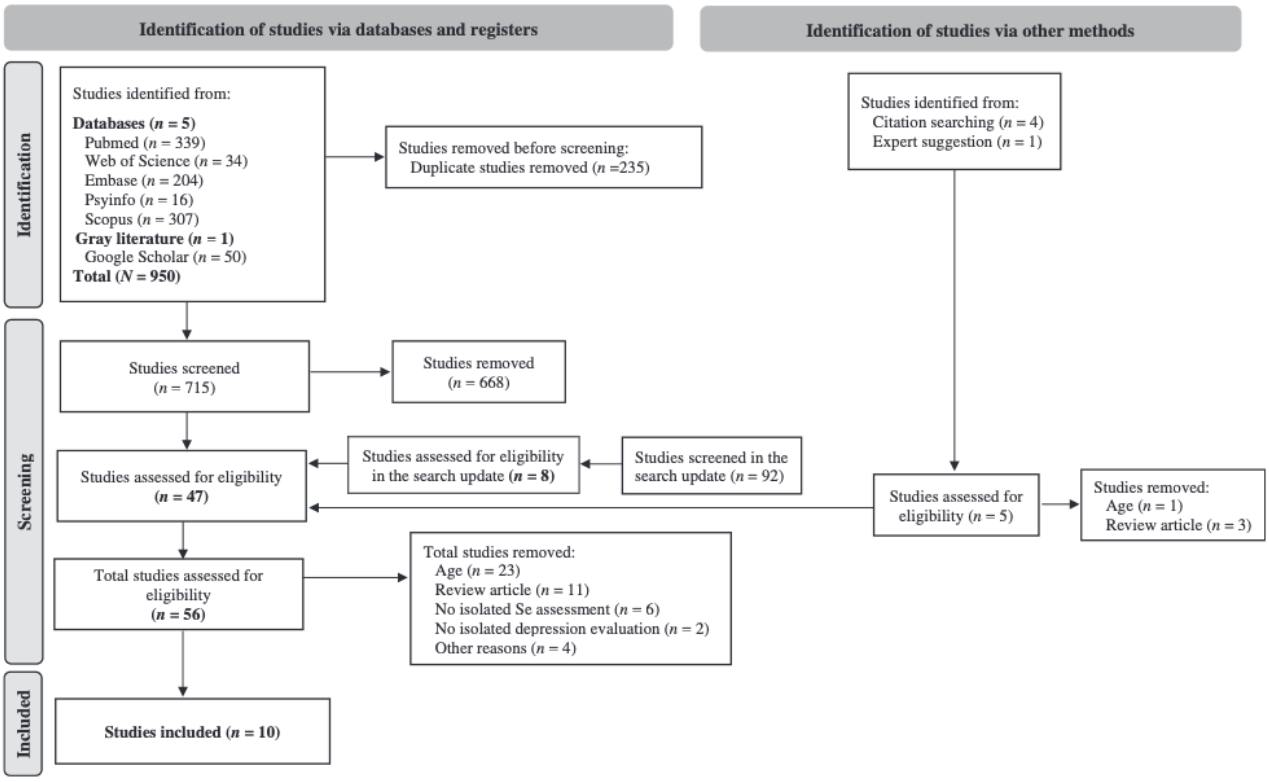

Figure 1 **Preferred Reporting Item for Systematic Reviews and Meta-Analyses (PRISMA) 2020 flow diagram for systematic reviews including searches of databases and registers only.** *Abbreviation*: Se, selenium. Adapted from Page et al.[12]

The studies by Colangelo et al[23] and Sánchez-Villegas et al[22] had 81.8% "Yes" answers in the checklist for cohort studies, and the study by Islam et al[26] had 80.0% "Yes" answers in the checklist for case-control studies.

The main sources of bias were related to the lack of clarity regarding the treatment of study groups[27,29] and whether (1) the groups were similar and recruited from the same population[22,23]; (2) the confusion factors and strategies to deal with them were identified[21,25,26]; (3) the study design was appropriate and deviations were considered[20]; (4) the strategies to deal with incomplete follow-up were adopted[23]; (5) the groups were similar at baseline[28]; (6) the researchers who investigated the outcomes were blinded to the treatment assignment[28]; (7) true randomization was used to assign participants to treatment groups, (8) the allocation to treatment groups was hidden, and (9) the investigator who administered the treatment was blinded to the treatment assignment.[27] Furthermore, for the cohort study, it was unclear whether participants were outcome-free at baseline or at the time of exposure, because reported information was collected at the beginning of the study and the questionnaire for the assessment of depression was used later.[22]

Selenium intake and depression

The 6 studies that examined dietary selenium intake predominantly compared their results to the American and Canadian recommended dietary allowances (RDAs) for selenium[22,24,25,30] or categorized them into quartiles or quintiles.[21,24] The average minimum and maximum intakes found were 28.15 μg/d[21] and 242 μg/d,[20] respectively. Because of the limited reported data, it was not possible to compare the percentage of individuals with adequate and inadequate intakes in observational studies.[21,22,24,25] However, 2 of the 4 studies[24,25] found similar results on the relationship between dietary selenium intake and depression, suggesting that adequate selenium intake is inversely proportional to the prevalence of depression or depressive symptoms. One such study found a mild negative correlation between daily selenium intake and depression score.[25]

Sánchez-Villegas et al[22] investigated various micronutrients for adequacy of intake in Spanish university students participating in the Seguimiento Universidad de Navarra (SUN) project who did not present with previous history or clinical diagnosis of depression, classifying them according to the number of nutrients with inadequate intake.[30] In that study, there was no association between selenium intake and depression risk at baseline (hazard ratio,: 1.22; 95% confidence interval [CI], 0.89–1.68) or after 10 years (hazard ratio, 1.29; 95% CI, 0. 94–1.78). Furthermore, when the dietary selenium intake of young adults (aged 20–31 y) was classified as higher or lower than the RDA, no

Table 2 **Studies on the impacts of selenium intake and status on symptoms of depression included in this systematic review**[20–29]

Reference	Sample, no.	Age, y	Country	Health status	Study design	Intervention/exposure	Comparison group	Selenium measures	Selenium intake or status tool	Outcome	Assessment or diagnostic tool	Study period	Findings
Finley and Penland (1998)[27]	30 men	18–45	USA	Healthy	RCT	Se-rich diet (189 ± 11 μg, mean ± SD) based on wheat products and high-Se beef and pork	Se-poor diet (21 ± 5.7 μg, mean ± SD)	Dietary intake, erythrocyte Se levels, and excretion	Direct food weighing/GFAAS/ICP-MS	Humor/depression diagnosis	POMS-Bi	105 d	Se absorption significantly ↑ the elated–depressed score in high Se group (107 ± 19; mean ± SD) compared with the low Se group (94 ± 14; mean ± SD, $P < 0.05$)
Hawkes and Hornbostel (1996)[20]	11 men	20–45	USA	Healthy	Double-blind RCT	Se-rich diet (356 μg/d) based on rice and beef samples obtained from soil very high in Se	Se poor-diet (13 μg/d)	Erythrocyte Se levels and dietary intake	Fluorometric technique with enhanced detection by HPLC	Humor	POMS-Bi	120 d	In the control group, the lower the initial Se status, the more the mood scores decreased. Se-rich diet did not improve mood.
Calissendorff et al. (2015)	38 men and women	18–55	Sweden	Graves' disease	Double-blind RCT	200 μg Se/d	Placebo tablets	SePP concentration	HPLC with ICP-MS	Depression	HADS, RPQ	36 wk	Se ↓ depression rate, with no difference from control. Depression score in the whole sample ↓ from 4.5 (range 0–15) to 2.0 (range 0–12), $P < 0.001$
Shor-Posner et al. (2003)[29]	63 men and women	24–53	USA	HIV	Double-blind RCT	200 μg Se/d	Placebo	Plasma Se levels	Standard fluorometric method	Psychological burden (anxiety, depression, and mood)	POMS-Bi	2 y	• No changes in depression prevalence • Psychological burden score ↓ (improved) in the Se (9%) and ↑ (13%) in the placebo groups
Sánchez-Villegas et al. (2017)[22]	13.983 men and women	18–55	Spain	Healthy	Cohort	Se adequacy in usual diet	NA	Dietary intake	Semi-quantitative FFQ	NA	*DSM IV*, *DSM V*	14 y of follow-up	Inadequate Se intake was not associated with an ↑ risk of developing depression (adjusted model[a]: HR, 1.29; 95%CI, 0.94–1.78)
Colangelo et al. (2014)[23]	3735 men and women	20–32	USA	Healthy	Cohort	Nail Se levels	NA	Nail Se levels	Neutron-activation analysis	Depressive symptoms	CES-D	25 y of follow-up	Doubled nail Se concentration was associated with a 56% ↑ in the odds of having depressive symptoms (OR, 1.56; 95%CI, 1.07–2.26)
Islam et al. (2018)[25]	495 men and women	18–44	Bangladesh	Healthy and with MDD	Case-control	NA	NA	Serum Se levels	FAAS/GFAAS	Major depression risk	*DSM V*	NA	Suggests that Se deficiency contributes to the MDD pathogenesis
Ferreira de Almeida et al. (2021)[21]	736 men and women	18–59	Brazil	Healthy or with depression	Cross-sectional	Usual dietary Se intake	NA	Dietary intake	24-h dietary recall	Depressive episodes	*DSM V*	NA	↑ Se intake associated with a 54% ↓ in the odds of developing depression (OR,

(continued)

Table 2 **Continued**

Reference	Sample, no.	Age, y	Country	Health status	Study design	Intervention/exposure	Comparison group	Selenium measures	Selenium intake or status tool	Outcome	Assessment or diagnostic tool	Study period	Findings
													0.46; 95%CI, 0.236–0.901)
Ghimire et al. (2018)[24]	7725 men and women	20–80, with a subsample of participants aged 20–31 y	USA	Healthy	Cross-sectional	Usual dietary Se intake and serum Se levels	NA	Dietary intake and serum Se levels	24-h dietary recall/HPLC with ICP-MS	Depressive symptoms	PHQ-9	NA	Individuals aged 32–80 y and with ↓ Se intake had ↑ chances of developing depressive symptoms. No changes were observed in individuals aged 20–31 y who did not reach minimum Se intake.
Shokati S et al. (2021)[25]	200 women	19–28	Iran	Helathy	Cross-sectional	Usual dietary Se intake	NA	Dietary intake	FFQ	Depression score	Beck anxiety questionnaire	NA	Intake of minerals such as Zn, Mg, and Se was negatively associated with the depression score

[a]Model adjusted for sex, age, physical activity, body mass index, energy intake, special diets, smoking, alcohol intake, and prevalence of cardiovascular diseases, hypertension, or type 2 diabetes mellitus.

Abbreviations: BDI, Beck's Depression Inventory; CES-D, Center for Epidemiological Studies depression scale; CI, confidence interval; *DSM-IV/V, Diagnostic and Statistical Manual of Mental Disorders, Fourth [or] Fifth Edition*; FAAS, flame atomic absorption spectrometry; FFQ, food frequency questionnaire; GFAAS, graphite furnace atomic absorption spectrometry; HADS, Hospital Anxiety and Depression Scale; HR, hazard ratio; HPLC, high performance liquid chromatography; ICP-MS, inductively coupled plasma mass spectrometry; MDD, major depressive disorder. Mg, magnesium; NA, data not available; OR, odds ratio; PHQ-9, Patient Health Questionnaire–9; POMS-Bi, Profile of Mood States Bipolar Scale; RCT, randomized controlled trial; RPQ, Rivermead Post-Concussions Symptom Questionnaire; Se, selenium; SePP, selenoprotein P; USA, United States of America; Zn, zinc.

association with depression risk was found (odds ratio [OR], 1.02; 95%CI, 0.41–2.51). Nevertheless, when the same approach was applied to individuals within the age range of 32–80 years, those who did not meet the RDA for selenium had a higher risk of depressive symptoms (OR, 1.77; 95%CI, 1.18–2.65) compared with those who met the RDA.[22]

Ferreira de Almeida et al[21] investigated dietary selenium intake and depression development through the evaluation of depressive episodes occurrence in male and female Brazilian farmers within the age range of 18–59 years who were resident in a region known for its horticulture production. This region is also known for its dietary pattern of mixing traditional Brazilian food with ultraprocessed foods and for its low fruit consumption, as well. When dietary selenium intake was classified into quartiles or quintiles, the probability of developing depressive episodes was lower when the dietary intake was higher. Comparison of the first (mean: $\leq$66.66 µg/d) and the last quartile (mean: >95.26 µg/d) revealed that individuals with more selenium intake had a smaller probability of developing depression, even after adjusting for sex, marital status, socioeconomic class, alcohol consumption, and pesticide poisoning (OR, 0.46; 95%CI, 0.23–0.90).[21]

Similar results were reported by Ghimire et al[24] in a subsample (n = 7725) of US residents aged $\geq$20 years who participated in the National Health and Nutrition Examination Survey between 2011 and 2014. Individuals with dietary selenium intake lower than the RDA were more likely to present depressive symptoms (OR, 1.57; 95%CI, 1.03–2.38) compared with those who reached the RDA. When the first (mean: $\leq$72.5 µg/d) and last quintiles (mean: >149.8 µg/d) of selenium intake were compared, participants in the highest quintile had a lower risk of developing depressive symptoms (OR, 0.60; 95%CI, 0.39–0.94).[24]

The results obtained from the 2 RCTs investigating the effects of selenium supplementation[20,27] differed from each other, with no improvement in the euphoric–depressive subscale score in 1 study[20] and an improvement in the other.[27] Hawkes and Hornbostel[20] evaluated the erythrocyte selenium concentration of 11 healthy men who were confined to a metabolic unit for 120 days. In the first 21 days, all participants were given a diet containing 80 µg of selenium/d. Subsequently, 1 group was fed 13 µg of selenium/d (control) and another group was fed 356 µg of selenium/d (intervention) until the 120th day. In general, no differences were observed in the mood scale score (POMS-Bi) between the study groups; however, in the control group, a positive correlation of the baseline selenium concentration with the elated–depressed and agreeable–hostile subscales ($r = 0.825$, $P = 0.043$; and $r = 0.954$,

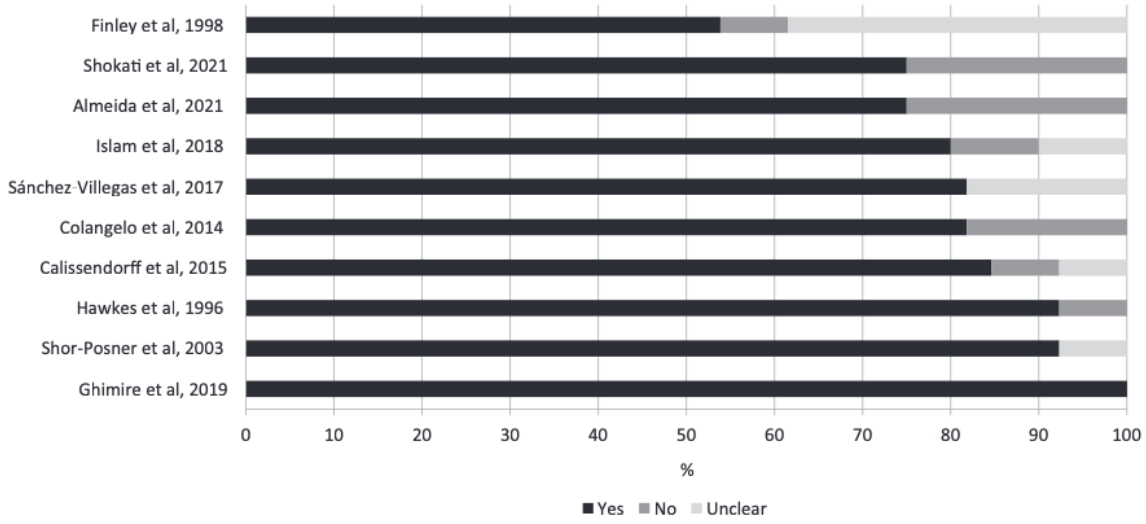

Figure 2 **Assessment of bias risk (percentage of answers to the Joanna Briggs Institute critical appraisal tools).**[20–29]

$P = 0.003$) was observed, suggesting that individuals with low selenium concentrations are more likely to experience depressed moods. Finley and Penland[27] placed 13 healthy men aged between 18 and 45 years either in an intervention group receiving a diet with 189 ± 11 µg selenium/d or in a control group receiving 21 ± 5.7 µg selenium/d (mean ± standard deviation [SD]) for 105 days. There was a significant decrease in the euphoric–depressive subscore in the intervention group compared with the control group (scores: 94 ± 14 vs 107 ± 19; mean ± SD, $P < 0.05$), which led to the improvement of the mood scores.

Shokati et al[25] investigated the relationship between the dietary intake of 3 micronutrients, 1 of which was selenium, with depression in 200 female Iranian university students. The mean daily intake (SD) of selenium was 106.52 (21.69) µg/d, which was classified as higher than the RDA. The authors found a mild negative relationship ($P < 0.001$; $r = 0.476$) between daily selenium intake and depression score.

Selenium status and depression

Six studies evaluated selenium concentration in blood samples,[20,24,26–29] and 1 study evaluated selenium concentration in nail samples.[23] In these studies, the mean selenium concentration ranged from 30 µg/L (in Bangladeshi patients with MDD)[26] to 194.1 µg/L (in healthy US individuals).[24]

In the study by Finley et al,[27] healthy US men who were placed on a high selenium diet (189 ± 11 µg/d; mean ± SD) for 105 days had increased erythrocyte selenium concentration (156 ± 3 ng/g at baseline and 163 ± 3 ng/g after 105 d; mean ± standard error), and improvement of mood as assessed by the POMS-Bi elated–depressed subscale (107 ± 19 points; mean ± SD) when compared with individuals in the control group (94 ± 14 points; mean ± SD).[27] Calissendorff et al[28] evaluated selenium status in terms of plasma selenoprotein P in 38 adults aged 18–55 years, 82% of whom were women who had been newly diagnosed with and were untreated for Graves' disease. Participants were evaluated for the presence of depression after recruitment. Afterward, they were randomly selected to receive either a placebo or 200 µg of selenium/d for 36 weeks. The concentration of plasma selenoprotein P increased from a median of 46.5 (interquartile range [IQR], 42–86 ng/mL) to 113.0 (IQR, 70–139 ng/mL; $P < 0.001$) in the intervention group. Furthermore, lower rates of depression were observed in the intervention group. However, no differences were observed in the placebo group.[28]

On the other hand, in the study by Shor-Possner et al,[29] the plasma selenium concentration of 32 men and 31 women living with HIV and a history of drug abuse did not increase in response to the supplementation of 200 µg of selenium/d for 12 months. However, these individuals were able to maintain the circulating concentration of selenium and had higher selenium concentration after 12 months compared with the placebo group (123.5 ± 23 vs 108.7 ± 15 µg/L, respectively; mean ± SD, $P = 0.002$). Although no significant changes were observed in the Beck's Depression Inventory score after the intervention, the treatment group had a 9% decrease in the Beck's Depression Inventory score compared with baseline (mean difference, −1.2), whereas the placebo group had a 13% increase compared with baseline (mean difference, +1.8). In addition, evaluation scores of the POMS scale were significantly lower ($P = 0.05$) in the intervention

group (9.7 ± 26; mean ± SD) compared with the placebo group (19.1 ± 19; mean ± SD) after the 12-month evaluation. In this study, the presence of depressive symptoms at baseline was not an exclusion criterion, and the use of drugs or current antiretroviral treatment was not significantly associated with depression.[29]

Hawkes and Hornbostel[20] also used the POMS-Bi scale and found a positive correlation between the baseline low erythrocyte selenium concentration with elated–depressed ($r = 0.825$; $P = 0.043$) and the pleasant–hostile ($r = 0.954$; $P = 0.003$) subscales in the control group. From this observation, the authors suggested that an initial marginal selenium deficiency may be necessary to properly observe mood changes in response to selenium consumption.[20]

Studies that evaluated individuals with and without depression showed that selenium concentrations were lower in those with depressive symptoms.[24,26] Islam et al[26] evaluated Bangladeshi individuals with MDD. It was suggested that the lower serum selenium concentration presented by the MDD group (0.03 ± 0.0002 mg/L; mean ± standard error mean [SEM]), compared with the healthy group (0.07 ± 0.003; mean ± SEM, $P < 0.05$), may be associated with the development of this disease. This may be because selenium prevents oxidative damage.[26] These findings align with the results reported by Ghimire et al[24] in which individuals with depressive symptoms had lower serum selenium concentration (median: 192.2 µg/L; IQR, 176.9–208.9 µg/L) than those without symptoms (median: 194.1 µg/L; IQR, 179.7–209.3 µg/L; $P = 0.003$).[24]

Colangelo et al[23] analyzed the connection between exposure to selenium and depressive symptoms in an experiment involving 3735 US residents (55% women) aged 18–30 years in the Coronary Artery Risk Development in Young Adults (CARDIA) study. The concentration of selenium was evaluated in nail samples, and a higher selenium concentration was associated with an increased risk of developing depressive symptoms (OR, 2.03; 95%CI, 1.12–3.70).[23] When the authors used the recommended Center for Epidemiological Studies Depression Scale score to achieve higher specificity in the evaluation of depressive symptoms (≥27), an OR of 1.59 in fifth quintile of nail selenium concentration (95%CI, 1.0–2.51) was obtained. However, when the researchers considered the standard cutoff point used in epidemiological studies (ie, ≥16 points), no association was found in any statistical model.[23]

From all the results described, it is possible to infer a high heterogeneity, mainly due to different methodological designs, methods for diagnosing depression and selenium assessment, and clinical conditions. As a result, we were not able to perform meta-analyses in this systematic review. Therefore, the associations between selenium intake or concentration with depression and its symptoms remain inconsistent.

DISCUSSION

We conducted a registered systematic review of current scientific evidence on the relationship between selenium and depression in adult individuals, which was carefully designed, following all the ethical and methodological criteria recommended for conducting this type of study. Although the number of studies was limited, most results indicated that low intake or blood concentration of selenium may be associated with depression or depressive moods and that adequate intake (from diet or supplementation) and blood concentration would be associated with a reduction in the occurrence of the symptoms of depression. However, the variability of information resulting from different methodological designs, methods to diagnose depression and to assess selenium status, and clinical conditions reported in the studies implies significant heterogeneity among them. As a result, a meta-analysis could not be performed, which makes it difficult to draw more accurate conclusions.

Studies included in this systematic review evaluated the status of selenium in plasma,[28,29] serum,[24,26] erythrocytes,[20,27] nails,[23] and diet,[20–22,27] which implies different interpretations. The evaluation of the serum or plasma concentration of selenium is performed mostly to reflect short-term levels,[31] whereas the measurement in erythrocytes shows intermediate levels (approximately up to 120 d).[31] The evaluation of selenium in nails, on the other hand, represents long-term levels, in addition to being a noninvasive and easier method. However, it lacks a reference value.[32] Although selenium is essential for the performance of numerous physiological processes, caution is required regarding intake recommendations and analysis. In addition to the assessment of micronutrient intakes being inherently difficult, differences in selenium concentrations in water and soils impose additional barriers that limit such evaluation.[33]

The low concentration of serum selenium observed by Islam et al[26] in patients with MDD, compared with healthy people, upholds the findings of this literature review on the pathogenesis of depression. This result suggests that deficient selenium concentrations could represent a risk factor for depressive mood, anxiety, and cognitive function decline, with significant involvement of antioxidant pathways[34] and association with reduced GPx-1, GPx-4, and thioredoxin reductase activity, which are important in the prevention of neuronal death activity.[10,35]

In addition to the antioxidant role, selenium seems to be related to depression in its modulation of thyroid hormones and neurotransmitters, such as dopamine and serotonin.[35,36] The selenoprotein family of

iodothyronine deiodinases is important for the synthesis of thyroid hormones; thus, dysregulation of thyroid function due to the deficiency of selenium may increase the risk of depression and other mood disorders.[37] Furthermore, selenium seems to be associated with the concentration of brain-derived neurotrophic factor in the brain. This neurotrophic factor is required for neuroplasticity and low levels influence the pathophysiology of depression.[38]

In this systematic review, we observed that selenium-rich diets were able to increase selenium plasma concentration in healthy individuals.[20,27] However, improvements in mood and symptoms of depression after intake of selenium-rich diets were only observed in individuals with low selenium intake, with no noteworthy results in selenium-repleted individuals.[20]

In this context, it is important to note that the different ways of analyzing selenium consumption in cross-sectional studies affected the results. When considering adequate or inadequate intake according to the RDA,[30] Ghimire et al[24] did not find a relationship between selenium consumption and depression. However, when Ferreira de Almeida et al[21] analyzed the data by quintiles, in which an upper limit above the RDA was assumed, important relationships between selenium intake and depressive episodes were observed. In the cohort study of Sánchez-Villegas et al,[22] none of the Spanish university students evaluated presented exclusive inadequacy of selenium consumption and there was no relationship between depression and selenium. In addition, Shokati et al[25] did not observe a sufficiently strong association between depression score and selenium intake in Iranian women, which can be explained by the average consumption above the recommended levels and a possible absence of selenium deficiency. All these results reinforce the hypothesis of the connection between selenium and depression as being dependent on dietary intake and/or biomarkers at adequate levels.

Two RCTs included in this systematic review evaluated individuals with pathological impairments (namely, Graves' disease, HIV).[28,29] Graves' disease is characterized by hyperthyroidism, which results in a significant alteration in the circulating concentration of the T3 and T4 hormones.[39] Selenium deficiency leads to a decrease in T4 to T3 conversion by iodothyronine deiodinases, which can exacerbate the disease.[35] According to Henley and Koehnle,[40] these hormones are significant in the monoaminergic neurotransmission process; therefore, they are important in the pathogenesis of depression. It is suggested that selenium therapy may benefit individuals with HIV and a history of drug abuse,[29] because a study conducted with rats found that GPx and catalase activities were decreased in response to oxidative stress induced by cocaine treatment.[41] Shor-Posner et al[29] and Calissendorff et al[28] observed that after receiving selenium supplementation, individuals with HIV or Graves' disease either maintained or increased plasma selenium concentrations and had decreased depression scale scores and depression rates compared with the nonsupplemented groups. These results, if replicated and validated, could guide the use of selenium as an adjuvant therapy with positive results in the treatment of psychological disorders in patients with these conditions.

It is important to mention that in the RCTs performed by Calissendorff et al[28] and Shor-Posner et al,[29] the researchers reported the use of L-selenomethionine for supplementation. Although the absorption pathways for selenium are still not completely understood, selenium in the forms of selenomethionine and selenocysteine appears to be well retained and more absorbed compared with selenate and selenite. Overall, most dietary selenium is highly bioavailable, with bioavailability of 90% and 100% for selenomethionine and selenocysteine, respectively, and 100% and 50% for selenate (with significant urinary losses) and selenite, respectively.[42,43] Therefore, the divergences in the RCTs' results cannot be attributed to the selenium chemical form but probably to other conditions inherent to the diseases.

The only study included in this systematic review that observed a positive association between selenium concentration and depressive symptoms used nails as a biomarker.[23] The temporal relationship between selenium exposure and the occurrence of depressive symptoms discussed by Colangelo et al[23] is a significant factor because the collection of nail samples was performed in 1987 and the depressive symptoms were evaluated in 1990, 1995, 2000, 2005, and 2010, which might have compromised the causality of the study.

In general, after analyzing the studies included in this systematic review, the hypothesis that selenium plays an important role in aspects related to depression and its symptoms could be considered. Interestingly, when performing the systematic-review search update, a systematic review and meta-analysis, recently published but not registered in PROSPERO, was found, in which the authors concluded that high selenium intake may have a protective role in postpartum depression and that supplementation with selenium may be effective in reducing depressive symptoms.[44] However, attention is drawn to some aspects of the study, such as the inclusion of adolescents, adult men and women (pregnant and postmenopausal), and the elderly. Different age groups and physiological states, as well as depression or depressive disorder assessment tools, intervention follow-up time, and study designs are

important characteristics that probably should not have been analyzed together, because many of them are not comparable. Therefore, it is important to reinforce the need for methodological rigor in systematic reviews and meta-analyses, because biased evidence can lead to potentially dangerous conclusions.

The role of selenium in various diseases has been extensively studied and it is suggested that supplementation in individuals without previous deficiency may be dangerous because it may increase the risk of diseases such as prostate cancer, type 2 diabetes mellitus, alopecia, and dermatitis.[45,46] Therefore, the same interpretation should be applied in the context of assessing the role of selenium in depression and other mental illnesses.

Several strengths of this systematic review can be underscored. We included studies with different methodological designs and covered current scientific evidence on the impacts of selenium in adult individuals with depression and its associated symptoms. It was carefully designed and followed all the recommended ethical and methodological protocols for systematic reviews. In addition, the studies included presented a high quality and a low risk of bias according to the recommended tools. Because the search by types of study was not restricted, it was possible to evaluate selenium in different ways (eg, through intake, blood and nail concentrations, and supplementation), which provided a wide range of information. Moreover, the evaluation of depression and depressive symptoms in the studies included in this systematic review was done using standardized instruments with validated scales and similarities regarding the disease genesis.

On the other hand, some limitations faced include the variability of instruments for diagnosing depression and selenium status, as well as differences in methodological designs and clinical conditions. However, the different methodological designs stemmed from the inclusion of more than 1 type of study, due to the scarcity of studies investigating the relationship between selenium and depression. All the particularities of the studies included in our systematic review increased the heterogeneity, which prevented us from performing meta-analysis and made it difficult to delineate more precise interpretations.

CONCLUSION

Evidence is lacking to confirm that selenium exerts positive effects on depression and depressive symptoms. Indeed, more studies are required to carefully evaluate the connection between this micronutrient and the development of depression. Much more accurate and standardized methods should be applied, considering better defined subclasses of selenium status, the different ways of evaluating selenium status and depression, as well as the individuals' clinical features.

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Availability of data and materials. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Supporting Information

The following Supporting Information is available in the online version of this article at the publisher's website.

Table S1 **Adapted searches for each of the databases**

Table S2 **Articles removed from the systematic review after comprehensive reading**

Table S3 **PRISMA checklist**

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