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Review Article

Iron; the Missing Link of Depression Prevention and Treatment: A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: To identify the effect of Iron as a preventive and therapeutic agent on depression and other hematological indices by a systematic review and meta-analysis.

Methods: International databases like Web of Science, PubMed, Cochrane, International Clinical Trials Registry Platform, Clinicaltrials.gov, and Scopus were searched until 27 July 2024 to identify eligible articles with the appropriate Medical Subject Headings (MeSH). The risk of bias tool for randomized trials (RoB 2) was used for precise assessment. Heterogeneity was determined using Cochran's Q-test and the I2 index. To assess source of heterogeneity, meta-regression was used. The pooled standardized mean difference (PSMD) was calculated by considering the random effects model.

Results: of 2154 studies,14 studies were included in systematic review and 6 studies were excluded from analysis due to lack of data for calculating PSMD and finally, 8 studies were included in meta-analysis. Based on the results, iron therapy led to improvement in depression symptoms (PSMD = -0.18; 95% CI: -0.32 to -0.03). The iron therapy led to increasing the blood level of Iron (PSMD = 0.57; 95% CI: 0.19 to 0.95), Ferritin (PSMD = 0.55; 95% CI: 0.25 to 0.85), HCT (PSMD = 0.40; 95% CI: 0.18 to 0.61), MCV (SMD = 0.67; 95% CI: 0.18 to 1.15) and Transferrin saturation (PSMD:0.26; 95% CI: 0.02 to 0.50). Based on the meta-regression result, the sample size, participant age, and publication year had no significant role in heterogeneity between studies.

Conclusion: The use of iron supplements in patients with depression can be considered. However, there is a need to conduct further studies involving various kinds of depression.

Introduction

Depression is a disabling disorder associated with reduced quality of life, medical comorbidity, and mortality. Over 300 million people live with depressive disorder.[1]

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Accordingly, depressive disorders are either lifelong or intermittent illustrated by sadness, loss of interest or pleasure, fatigue or loss of energy, low self-esteem, insomnia, low mood, suicidal thoughts, or drowsiness. Several biological processes and pathways such as inflammation, oxidative stress, and progressive neuropathology play a key role in depression.[2] Unfortunately, it is predicted that depression will continue to rise until 2030 and will be the leading cause of illnesses after AIDS/ HIV.[3] the prevalence of depression is reported 42.59%in Iranian population.[4] However, it is hypothesized that serotonin deficiency is directly correlation with depression. Therefore, antidepressants, especially serotonin reuptake inhibitors (SSRIs), are prescribed to attenuate depression symptoms. However, the probable side effects of antidepressants should be taken into consideration Normally, antidepressants act by increasing levels of dopamine, noradrenaline, and serotonin.[5] However, even the most common antidepressants have long-term side effects. Besides,over time,patients will need higher doses of these kinds of drugs. Also, current antidepressants have been shown to be ineffective only in 50% of patients.[6]

In addition, about one-third of patients are unable to give up medication. Furthermore, about 50% of patients do not respond to antidepressants for the first time.Meanwhile, it is obvious that new treatment options for depression must be developed.[7] On the other hand, iron is an essential element in the body that plays an important role in brain development and human physiological functions. For instance, the transport of oxygen, the synthesis and repair of DNA as well as the transport and metabolism of neurotransmitters are among the functions of iron in the body.[8] Reduction in the body iron not only causes the accumulation of monoamine oxidase, which significantly reduces catechol transmitters, but also prevents the loss of serotonin and reduces the volume and activity of dopamine.[9] Furthermore, excessive iron storage can prevent the synthesis of dopamine by inducing toxic free radicals.[10] Additionally, Iron is a cofactor of hydroxylase enzymes. The role of these enzymes is to limit the synthesis of dopamine, serotonin norepinephrine both directly and indirectly. It is worth noting that the balance between these three neurotransmitters determines the presence or absence of depression. Therefore, the presence of iron is essential for the synthesis of neurotransmitters.[11] Meanwhile, in severe depression, cytokine-based neuroinflammation reduces the production of neurotransmitters and causes iron deficiency in the brain.[12] Also, evidence suggests that iron supplementation may be effective in controlling the stress and depression among mothers with iron deficiency.[13]

Up to now, no meta-analysis has been performed on the effectiveness of iron supplementation for depression. Therefore, we will conduct a comprehensive systematic review and meta-analysis to investigate the current evidence on the effect of iron on the prevention and treatment of depression.

Methods

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were observed in the report of the study. This study was registered on PROSPERO by “CRD42022328940” ID.

Search strategy

We searched Cochrane, Web of Science(WoS), PubMed, Scopus, International Clinical Trials Registry Platform and Clinicaltrials.gov until 27 July 2024 to identify eligible articles impact of iron on depression with the appropriate medical terms (Figure1). In addition, Google scholar was used to accessing grey literature. MESH keywords are seen on appendix 1.

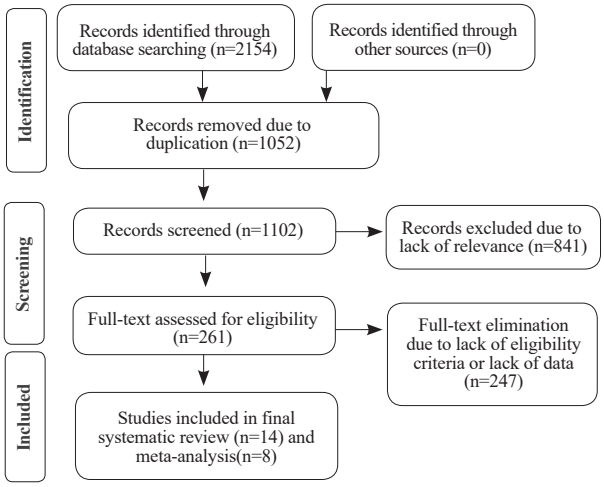

Figure 1. Flow diagram of study selection

Eligible Criteria

Types of studies

All randomized controlled trials that evaluated the effect of iron supplement for the treatment of depression were eligible for systematic review.

Types of participants

This review included trials involving adult individuals suffering from depression who were treated by iron supplements. Further, the patients under 18 were excluded. Participants who received a medication other than iron supplementation, were excluded.

Types of interventions

Trials were considered if they studied administration of iron supplement of any dosage, route or regimen for the treatment of depression and compared it with any other therapeutic interventions.

Types of outcome measures

The relative effects of iron supplement were estimated according to the score of depression improvement and hematological outcomes.

Data collection

Two authors independently selected studies for inclusion. Any disagreement between review authors is resolved by discussion or, if necessary, it was done by involving a third review author. The excluded studies are listed along with the reasons for the exclusion. All related articles in full text were searched. If the content of studies was vague, the authors were directly asked for explanation.

Data extraction

Two authors independently entered the desired data in a special form dedicated to further review. The items were as following: author, year, location, design, participants, age, depression score, iron therapy details, and other secondary outcomes including the level of blood indices like ferritin, iron, hemoglobin(HB),hematocrit (HCT), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), Red Blood Cell(RBC),transferrin, transferrin saturation, albumin, and 25(OH)D.

Risk of bias

the criteria mentioned in the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) was used for precise assessment. Meanwhile, five domains were assessed: risk of bias arising from the randomization process; risk of bias owing to deviations from the intended interventions; missing outcome data; measurement of the outcome; and selection of the reported result.[14]

Statistical Analysis

Mean and standard deviation(SD) of depression score and hematological variables in the iron intervention and control group was extracted and if Median and IQR was reported; we changed it to mean with [(min + max + 2*Median)/4] or [(med + q1 + q3)/3] and SD with [IQR/1.35]. Then change score of depression and hematological variables in each group was calculated by mean after minus before. Then, standard deviation in randomized control trial was calculated based on formulas (1) and (2):

$$SD_{\text{change score}} = \sqrt{SD_{\text{before}}{}^2 + SD_{\text{after}}{}^2 - \left(2 \times r \times SD_{\text{before}} \times SD_{\text{after}}\right)}$$

Where SD_{before}, SD_{after}, and Corr is the standard deviation in before intervention, standard deviation after intervention, and correlation coefficient between before and after.

Formula 2:

$$SD_{pooled} = \sqrt{\frac{(n_1 - 1)SD^2_{intervention} + (n_2 - 1)SD^2_{control}}{n_1 + n_2 - 2}}$$

Where $SD_{intervention}$, $SD_{control}$, n_1, and n_2 are the standard deviation in the intervention group, the standard deviation in the control group, and the sample size in the intervention and control groups. Then the pooled standardized mean difference (PSMD) was calculated by the "Metan" command. If the PSMD is positive, it will be in favor of the intervention and vice versa. We used the Cochran's Q-test to explore the heterogeneity of included studies with a significant alpha level of 0.05. We also measured heterogeneity using the I^2 statistic to quantify inconsistencies. The I^2 values above 0.5 were considered as a substantial heterogeneity.[15] To estimate PSMD for depression score and other hematological variables the fixed-effect model was used, and when the heterogeneity was greater than 0.5, the random-effects model was used. The meta-regression analysis was used to examine the effect of study design, sample size, age, and publication year as factors affecting heterogeneity among studies. The "Meta bias" command and Begg's test were used to check for publication bias, and if there was any publication bias, the PSMD was adjusted with the "Metatrim" command using the trim-and-fill method. In all analyses, a significance level of 0.05 was considered.

Results

Searching of databases yielded 2154 studies. Afterward, redundant papers were excluded, finally, 14 studies were included in the systematic review and 8 studies were included in the meta-analysis (Figure 1). In total, 4815 and 2982 participants were included in the systematic review, and meta-analysis; respectively. The study characteristics are available in Table 1.

Table 1. Contextual details of included studies in systematic review

ID	Author (ref)	Year	Country	Design	Gender (n)	Age (year)	Intervention form, dosage, frequency	Trial time	Control	Measure	Situation
1	Calje et al.[33]	2024	New Zealand	Randomized controlled trial	Female n=26	29.7±6.0	(A) IV iron (1000 mg ferric carboxymaltose single dose) (B) RBCT	12 weeks	(C) IV-iron and RBC-T	self-reported questionnaire	Excluded
2	Kapoor et al.[34]	2023	Japan	Randomized controlled trial	Female (n=42), male (n=49)	28.2±0.8	Oral Iron 3.6 mg daily	4 weeks	Placebo	POMS VAS	Included
3	Tavcar et al.[35]	2023	Slovenia	Randomized clinical trial	Female n=278	31±4	(A) IV ferric carboxymaltose (1000 mg, single dose) (B) IV ferric derisomaltose (1500 mg, single dose)	6 weeks	(C) Oral ferrous sulphate; two 80 mg; daily	EPDS	Excluded
4	Vafa et al.[37]	2019	Iran	Randomized controlled trial	Female n=74	39.25	Oral Vit D and iron 1000 IU/d Vit D plus 27 mg/d iron	12 weeks	Vit D plus placebo	BDI BAI	Included
5	Holm et al.[38]	2019	Denmark	Randomized controlled trial	Female n=85	32.5	IV iron isomaltoside, 1200 mg six times within 12 weeks	12 weeks	Oral iron	MFI EPDS	Excluded
6	Stewart et al.[30]	2017	Malawi	Randomized controlled trial	Female n=1391	24.5±6	LNS daily dose (20 g) was designed to contain the same micronutrients as the MMN capsules, plus 4 additional minerals, protein, and fat	6 months	IFA(60mg iron and 400-µg folic acid); MMN(IFA plus 16 micronutrients	SRQ EPDS	Excluded
7	Holm et al.[21]	2017	Denmark	Randomized controlled Trial	Female n=196	32.4±4.5	IV iron isomaltoside, 1200 mg six times within 12 weeks	12 weeks	Oral iron	MFI EPDS	Excluded
8	Sheikh et al.[27]	2017	Iran	Randomized controlled trial	Female n=70	31.8±4.8	Oral Elemental iron 50 mg once daily	6 weeks	Placebo	EPDS	Included

9	Nguyen et al.[39]	2017	Vietnam	Randomized controlled trial	Female n=1616	25.9±4.3	(A) iron and folic acid (IFA, 2800 µg FA+ 60 mg iron) (B) multiple micronutrients (MM, 15 micronutrients including 2800 µg FA+ 60 mg iron)	12 weeks	folic acid 2800 µg control	CES-D EPDS	Included
10	Perello et al.[40]	2014	Spain	Randomized controlled trial	Female n=60	29.7±5.5	IV ferrous sucrose 200 mg/24 hrs for two days	6 weeks	Placebo	EPDS STAI	Included
11	Vaucher et al.[41]	2012	France	Randomized controlled trial	Female n=198	36.85±9.4	Oral prolonged-release ferrous sulfate,80 mg, once daily	12 weeks	Placebo	VAS CAPPS	Included
12	Nguyen et al .[42]	2009	Guatemala	Randomized controlled trial	Female n=369	31.1±9.3	A) multiple micronutrients (MM) C) folic acid (FA) weekly (5,000 or 2,800µg) or daily (400 or 200 µg) folic acid plus iron, zinc, and vitamin B12	12 weeks	B) iron and folic acid (IFA)	CES-D	Excluded
13	Gariballa et al. [43]	2007	UAE	Randomized controlled trial	Female n=225	75.6±5.95	Two bottles (200 mL each) of an oral nutritional supplement containing iron, twice daily	6 weeks	Placebo	GDS AMT[9]	Included
14	Verdon et al.[44]	2003	Switzerland	Randomized controlled trial	Female n=136	35.35±10.7	Oral ferrous sulfate 80 mg, once daily	4 weeks	Placebo	VAS	Included

EPDS, Edinburgh postnatal depression scale; BDI, Beck's depression inventory; VAS, Visual analogue scale; CAPPS, Current and past psychological scale; CES-D, Center for epidemiologic studies depression scale; STAI, State-trait anxiety inventory; SRQ, Self-reporting questionnaire; GDQ, Geriatric depression questionnaire; AMT, Abbreviated mental test questionnaire; BAI, Beck anxiety inventory; MFI, Multidimensional fatigue inventory; RBC-T, Red blood cell transfusion; IV, Intravenous; Vit, Vitamin; IFA, Iron-folate; MMN, Multiple-micronutrient; LNS, Lipid-based nutrient supplement; POMS, Profile of mood state.

Heterogeneity and pooled estimations

There was significant heterogeneity between different studies for the effect of iron on depression (Cochran's Q-test P-value < 0.001) so the I2 index was above 60% overall.
The results of the study's analysis of the PSMD by study design were presented in Figure 2. Due to high heterogeneity, the random effects model approach was used The results of meta-analysis revealed that the overall PSMD was -0.18 (-0.32 to -0.03). In simpler terms, the mean score in the intervention group was significantly lower than in the control group, indicating that iron had a positive impact on managing depression. Result of present study also showed that the iron therapy led to increase the blood level of Iron (PSMD = 0.57; 95% CI: 0.19 to 0.95), Ferritin (PSMD = 0.55; 95% CI: 0.25 to 0.85), Hct (PSMD = 0.40; 95% CI: 0.18 to 0.61), MCV (SMD = 0.67; 95% CI: 0.18 to 1.15) and Transferrin saturation (PSMD:0.26; 95% CI: 0.02 to 0.50). the PSMD for hematological outcomes was showed in Table 2 and Figure 3.

Risk of bias

According to RoB 2, plus sign (+) indicates low risk of bias; minus sign (−) indicates high risk of bias and question mark(?) indicates unclear of bias. Judgments are based on and summaries the answers to signaling questions (appendix 2).

Univariate Meta-regression analysis

Table 3 shows the meta-regression results to investigate the effect of sample size, participant age, and publication year on heterogeneity between studies Accordingly, none of the variables had a significant role

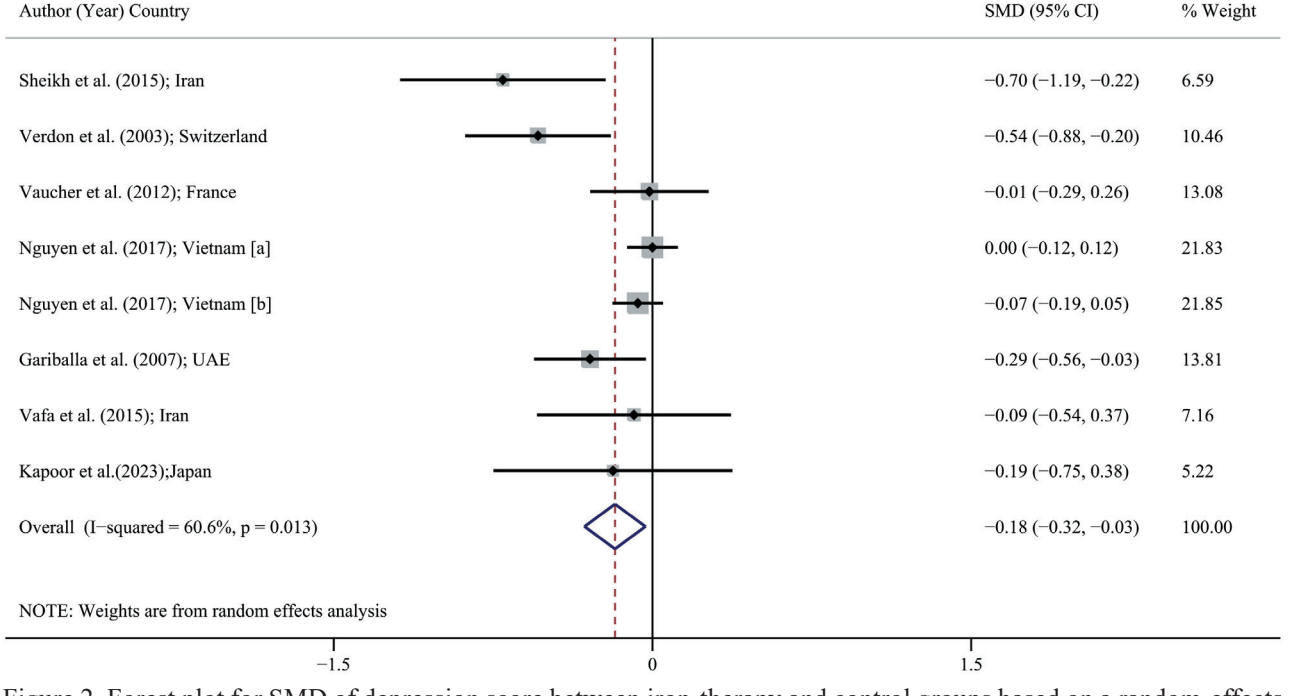

Figure 2. Forest plot for SMD of depression score between iron-therapy and control groups based on a random-effects model.

Table 2. Pooled standardized mean difference and corresponding 95%CI

Hematological variables	N; p-value of heterogeneity; I^2 value	PSMD (95% CI)
Iron	n=3; p=0.22; I^2 = 0.339	0.55 (0.25 to 0.85)*
Ferritin	n=4; p=0.004; I^2 = 0.778	0.55 (0.25 to 0.85)*
Red Blood Cells (RBC)	n=1; p= ---; I^2 = ---	0.15 (-0.13 to 0.43)
Hemoglobin (Hb)	n=9; p= 0.079; I^2 = 0.433	0.04 (-0.05 to 0.13)
Hematocrit (Hct)	n=3; p= 0.379; I^2 = 0	0.40 (0.18 to 0.61)*
Mean Corpuscular Volume (MCV)	n=1; p= ---; I^2 = ---	0.67 (0.18 to 1.15)*
Mean Corpuscular Hemoglobin (MCH)	n=1; p= ---; I^2 = ---	0.37 (-0.11 to 0.84)
Transferrin	n=2; p<0.001; I^2 = 0.969	0.27 (-0.84 to 1.38)
Transferrin saturation	n=1; p= ---; I^2 = ---	0.26 (0.02 to 0.50)*
Albumin	n=1; p= ---; I^2 = ---	0.14 (-0.12 to 0.41)
25(OH)D	n=1; p= ---; I^2 = ---	-0.06 (-0.52 to 0.39)

PSMD, Pooled standardized mean difference

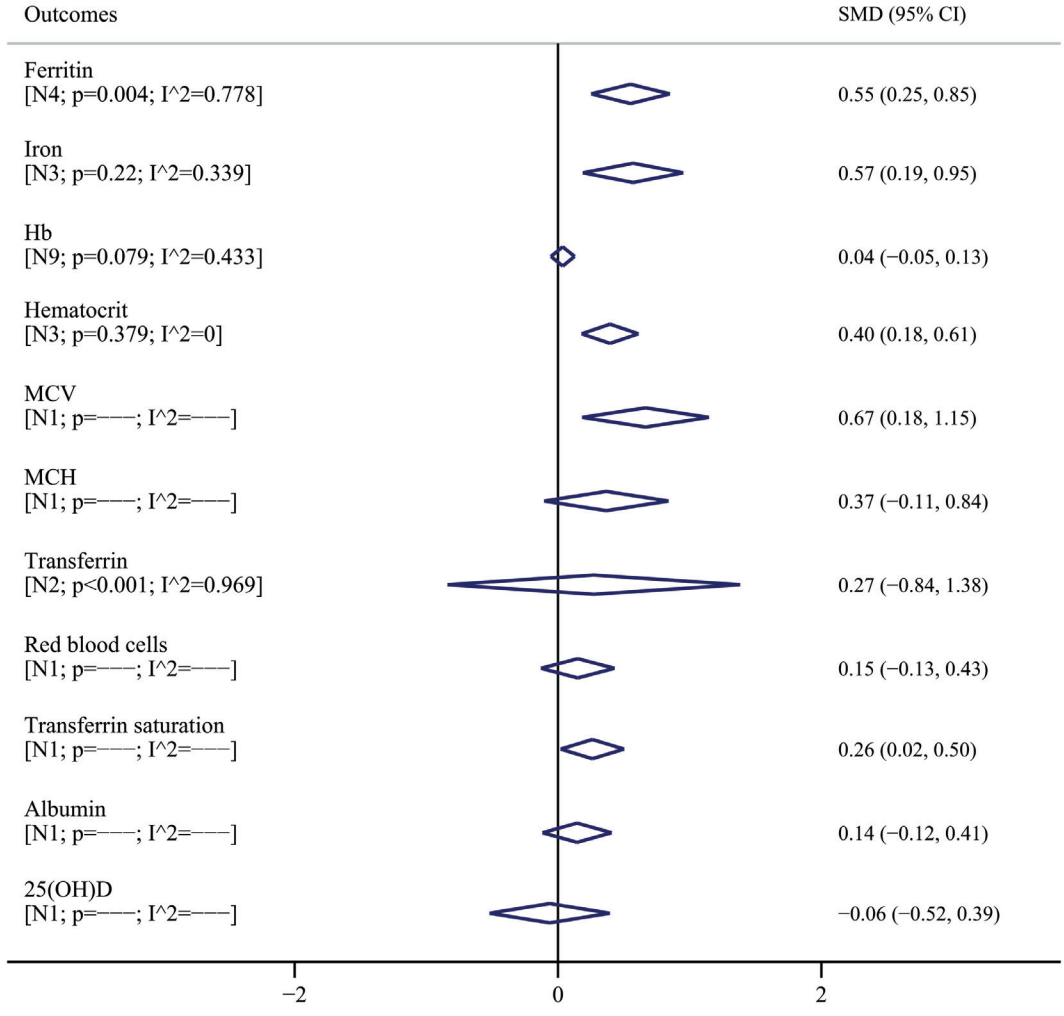

Figure 3. PSMD and 95% CI of the effect of iron therapy on hematological variables.

Table 3. The univariate meta-regression analysis

Variables	Coefficient	95% CI	p-value
Sample size	0.001	-0.001 to 0.001	0.086
Participant age	-0.003	-0.017 to 0.010	0.529
Publication year	0.026	-0.002 to 0.055	0.066

CI, Confidence interval

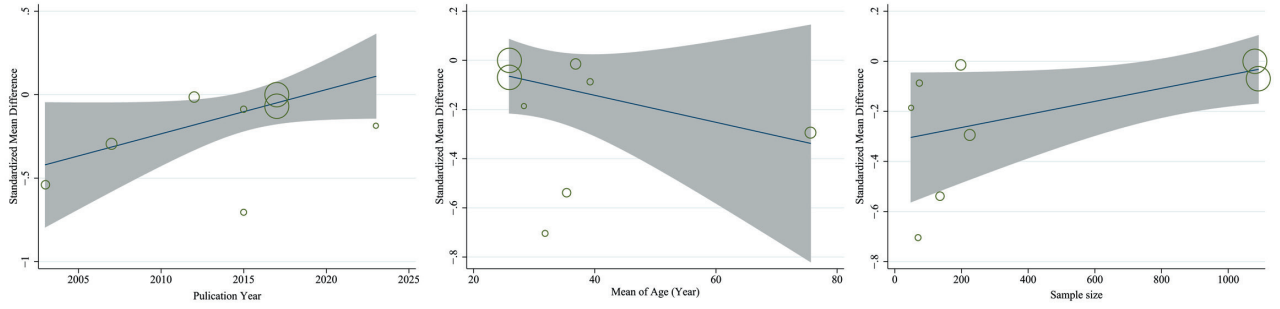

Figure 4. Scatter plot and linear regression line of between Standardized mean difference (SMD) of depression score with publication year, mean age of participants and sample size using meta-regression

on heterogeneity between studies. The figure 4 showed the result of univariate meta-regression between PSMD and heterogeneity predictors. The size of the circles indicates the precision of each study. As showed in figure 4, there is no significant association concerning the pooled SMD of depression score with age, publication year and sample size.

Publication bias

Based on the results of Begg's test, there was no significant publication bias for the effect of iron on depression in our study. (Z score: -1.24; p: 0.216).

Discussion

Based on the results of this review, iron therapy led to improvement in depression symptoms.In line with the results of current review,Berthou et al.(2022) conducted a review that it was proved either oral or IV-iron compounds can attenuate the depression symptoms.[16] A review study by Wassef et al., (2019) showed that both anemia and iron deficiency can lead to PPD in high-risk women.[17] However, Beard et al., (2005)confirmed in their study that iron supplement can hinder depressive symptoms in PDD patients.[13] Another study conducted by Bergis et al., (2019) confirmed that iron deficiency is in direct relation with depressive behaviors in diabetic patients.[12] Moreover, Khanna et al., (2019) showed that iron deficiency anemia is directly related to depression, fatigue and lack of emotion. Additionally, major depressive disorder is correlated with inflammation and changes in iron levels.[18] Li et al., (2018) performed a study in more than 14834 adults which confirmed that zinc, iron, selenium and copper uptake was lower in individuals with depression. Besides, iron therapy lead to a decrease in depression symptoms.[19] Duan et al., (2021) confirmed that there is iron deficiency in the basal ganglia of people with depression, but iron deficiency was

not significant in the cortex. Also,severe iron deficiency in the putamen and thalamus was observed. In the group of depressed patients, there was an increased magnetic susceptibility in the thalamus and lateral putamen.[20]

As iron deficiency is a source of depression symptoms, researchers compared the effectiveness of iron supplementation depending on the route of administration. Previous studies hypothesized that an IV iron injection would be more effective than daily oral administration on symptoms of depression. Likewise. Holm et al., (2017) showed that IV-iron can have significant effect on diminishing physical fatigue among participants.[21] Albacar et al., (2011) reported that iron play an important role in the etiology of PPD.[22] Similarly, Dama et al., (2018) showed women who were suffering from deficiency of iron, had higher rate of depression.[23] Also, a study by Månsson et al., (2005) proved that iron supplementation can reduce depressive symptoms.[24] Regarding hematological factors, a study by Chandrasekaran et al., (2018) approved that Hb level in PPD patients was nor lower than the group who did not have PPD;[25] this finding is in line with results of our study.Moreover, Vahdat Shariatpanaahi et al., (2007) showed that average level Hb is lower in the depressed group, as it is not in line with the results of our study.[26] Likewise, a trial by Sheikh et al., (2017) showed after iron therapy, simultaneous increased level of ferritin and improved depressive symptoms were observed in the iron therapy group, which is consistent with the results of current study.[27] Shafi et al., (2018) published a study after defining the relation between iron deficiency and depression.Interestingly, the Hamilton depression rating scale was utilized to evaluate the level of depression, as such scale hadn't been used in included studies of this review. Then, it was confirmed that Hb level was lower in depressed individuals compared with control group.[28]

Additionally, another study demonstrated that the lower serum ferritin and Hb level found, the more depressive symptoms observed.[29, 30] Further,reseaercher proved in their study that postpartum anemia and lower Hb levels are associated with incidence of PPD.[31] Therefore, dietary issues should be considered. Nevertheless, it is worth noting due to the specific property of iron, it can be used as a therapeutic agent for depression. On the other hand, drugs in the form of nanoparticles can penetrate into deeper layers,show higher anti-inflammatory effects and improve the effectiveness of the treatment.Moreover, the role of iron in the treatment of depression with taking advantage of nanotechnology should be addressed. For instance, Khadrawy et al., (2021) evaluated the antidepressant effect of iron oxide nanoparticles in combination with curcumin and proved that the mentioned mixture can show antidepressant effect, as it is in can regulate neurotransmitter level as well as stopping oxidative stress.[32]

Limitation

The tools were different for the assessment of depression and because these tools were varying, it’s not possible to effect of that on heterogeneity. Also, we aimed to include effect of ethnic on our outcomes, but due to low number of studies, it was not possible to estimate robustly.

Conclusion

Iron therapy can lead to the prevention and treatment of depression. Furthermore, future studies should focus on a wider range of male participants as well as evaluating various kinds of depression other than PPD.

Conflict of Interests

The authors declare no conflict of interests.

Ethics approval

This study was approved by the ethical code IR.ABZUMS.REC.1401.024.

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References

1. Khune AA, Rathod HK, Deshmukh SP, Chede SB. Mental health, depressive disorder and its management: A review. GSC Biological and Pharmaceutical Sciences. 2023;25(2):001-13.

2. Moylan S, Maes M, Wray N, Berk M. The neuroprogressive nature of major depressive disorder: pathways to disease evolution and resistance, and therapeutic implications. Molecular psychiatry. 2013;18(5):595-606.

3. Weinberger AH, Gbedemah M, Martinez AM, Nash D, Galea S, Goodwin RD. Trends in depression prevalence in the USA from 2005 to 2015: widening disparities in vulnerable groups. Psychological medicine. 2018;48(8):1308-15.

4. Mohamadi M, Mohaqeqi Kamal SH, Vameghi M, Rafiey H, Setareh Forouzan A, Sajjadi H. A meta-analysis of studies related prevalence of depression in Iran. Journal of Research and Health. 2017;7(1):581-93.

5. Strawn JR, Geracioti L, Rajdev N, Clemenza K, Levine A. Pharmacotherapy for generalized anxiety disorder in adult and pediatric patients: an evidence-based treatment review. Expert opinion on pharmacotherapy. 2018;19(10):1057-70.

6. Pattanayak RD, Sagar R. Depressive Disorders in Indian Context: A Review and Clinical Update for Physicians. The Journal of the Association of Physicians of India. 2014;62(9):827-32.

7. O'Leary OF, Dinan TG, Cryan JF. Faster, better, stronger: towards new antidepressant therapeutic strategies. European journal of pharmacology. 2015;753:32-50.

8. Muhoberac BB, Vidal R. Iron, ferritin, hereditary ferritinopathy, and neurodegeneration. Frontiers in neuroscience. 2019;13:1195.

9. Burhans MS, Dailey C, Beard Z, Wiesinger J, Murray-Kolb L, Jones BC, et al. Iron deficiency: differential effects on monoamine transporters. Nutritional neuroscience. 2005;8(1):31-8.

10. Bagnato F, Hametner S, Yao B, van

Gelderen P, Merkle H, Cantor FK, et al. Tracking iron in multiple sclerosis: a combined imaging and histopathological study at 7 Tesla. Brain. 2011;134(12):3602-15.

11. Saeidienik F, Shahraki MR, Fanaei H, Badini F. The effects of iron oxide nanoparticles administration on depression symptoms induced by LPS in male wistar rats. Basic and Clinical Neuroscience. 2018;9(3):209.

12. Bergis D, Tessmer L, Badenhoop K. Iron deficiency in long standing type 1 diabetes mellitus and its association with depression and impaired quality of life. Diabetes research and clinical practice. 2019;151:74-81.

13. Beard JL, Hendricks MK, Perez EM, Murray-Kolb LE, Berg A, Vernon-Feagans L, et al. Maternal iron deficiency anemia affects postpartum emotions and cognition. The Journal of nutrition. 2005;135(2):267-72.

14. Higgins JP, Savović J, Page MJ, Elbers RG, Sterne JA. Assessing risk of bias in a randomized trial. Cochrane handbook for systematic reviews of interventions. 2019:205-28.

15. Deeks J. Analysing data and undertaking meta-analyses. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor (s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.4 (updated August 2023). Cochrane, 2023. Available from training cochrane org/ handbook. 2023.

16. Berthou C, Iliou JP, Barba D. Iron, neuro-bioavailability and depression. EJHaem. 2022;3(1):263-75.

17. Wassef A, Nguyen QD, St-André M. Anaemia and depletion of iron stores as risk factors for postpartum depression: a literature review. Journal of Psychosomatic Obstetrics & Gynecology. 2019;40(1):19-28.

18. Khanna P, Chattu VK, Aeri BT. Nutritional aspects of depression in adolescents-a systematic review. International journal of preventive medicine. 2019;10.

19. 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. Journal of affective disorders. 2018;228:68-74.

20. Duan X, Xie Y, Zhu X, Chen L, Li F, Feng G, et al. Quantitative susceptibility mapping of brain iron deposition in patients with recurrent depression. Psychiatry Investigation. 2022;19(8):668.

21. Holm C, Thomsen L, Norgaard A, Langhoff-Roos J. Single-dose intravenous iron infusion or oral iron for treatment of fatigue after postpartum haemorrhage: a randomized controlled trial. Vox sanguinis. 2017;112(3):219-28.

22. Albacar G, Sans T, Martín-Santos R, García-Esteve L, Guillamat R, Sanjuan J, et al. An association between plasma ferritin concentrations measured 48 h after delivery and postpartum depression. Journal of affective disorders. 2011;131(1-3):136-42.

23. Dama M, Van Lieshout RJ, Mattina G,

Steiner M. Iron deficiency and risk of maternal depression in pregnancy: an observational study. Journal of Obstetrics and Gynaecology Canada. 2018;40(6):698-703.

24. Månsson J, Johansson G, Wiklund M, Baigi A, Marklund B. Symptom panorama in upper secondary school students and symptoms related to iron deficiency Screening with laboratory tests, questionnaire and interventional treatment with iron. Scandinavian journal of primary health care. 2005;23(1):28-33.

25. Chandrasekaran N, De Souza LR, Urquia ML, Young B, Mcleod A, Windrim R, et al. Is anemia an independent risk factor for postpartum depression in women who have a cesarean section?-A prospective observational study. BMC Pregnancy and Childbirth. 2018;18:1-7.

26. Vahdat Shariatpanaahi M, Vahdat Shariatpanaahi Z, Moshtaaghi M, Shahbaazi S, Abadi A. The relationship between depression and serum ferritin level. European journal of clinical nutrition. 2007;61(4):532-5.

27. Sheikh M, Hantoushzadeh S, Shariat M, Farahani Z, Ebrahiminasab O. The efficacy of early iron supplementation on postpartum depression, a randomized double-blind placebo-controlled trial. European journal of nutrition. 2017;56:901-8.

28. Shafi M, Taufiq F, Mehmood H, Afsar S, Badar A. Relation between depressive disorder and iron deficiency anemia among adults reporting to a secondary healthcare facility: a hospital-based case control study. J Coll Physicians Surg Pak. 2018;28(6):456-559.

29. Stewart R, Hirani V. Relationship between depressive symptoms, anemia, and iron status in older residents from a national survey population. Psychosomatic medicine. 2012;74(2):208-13.

30. Stewart RC, Ashorn P, Umar E, Dewey KG, Ashorn U, Creed F, et al. The impact of maternal diet fortification with lipid-based nutrient supplements on postpartum depression in rural Malawi: a randomised-controlled trial. Maternal & child nutrition. 2017;13(2):e12299.

31. Alharbi AA, Abdulghani HM. Risk factors associated with postpartum depression in the Saudi population. Neuropsychiatric disease and treatment. 2014:311-6.

32. Khadrawy YA, Hosny EN, Magdy M, Mohammed HS. Antidepressant effects of curcumin-coated iron oxide nanoparticles in a rat model of depression. European Journal of Pharmacology. 2021;908:174384.

33. Caljé E, Oyston C, Wang Z, Bloomfield F, Marriott J, Dixon L, et al. The fatigue after infusion or transfusion pilot trial and feasibility study: A three-armed randomized pilot trial of intravenous iron and blood transfusion for the treatment of postpartum anemia. Transfusion. 2024;64(2):301-14.

34. Kapoor MP, Sugita M, Kawaguchi M, Timm D, Kawamura A, Abe A, et al. Influence of iron supplementation on fatigue, mood states and sweating profiles of healthy non-anemic athletes during a training exercise: A

double-blind, randomized, placebo-controlled, parallel-group study. Contemporary Clinical Trials Communications. 2023;32:101084.

35. Tavčar LB, Hrobat H, Gornik L, Velikonja VG, Lučovnik M. Incidence of postpartum depression after treatment of postpartum anaemia with intravenous ferric carboxymaltose, intravenous ferric derisomaltose or oral ferrous sulphate: A randomized clinical trial. European Journal of Obstetrics & Gynecology and Reproductive Biology: X. 2023;20:100247.

36. Maryam B, Basharat S, Gilani S, Qamar M, Basharat A, Basharat B. Iron supplementation intermittently in reducing the severity of depression. American Scientific Research Journal for Engineering, Technology, and Sciences (ASRJETS). 2020;69(1):167-74.

37. Vafa M, Azizi-Soleiman F, Kazemi SM, Salehi M, Zaeri F, Abiri B, et al. Comparing the effectiveness of vitamin D plus iron vs vitamin D on depression scores in anemic females: Randomized triple-masked trial. Medical Journal of the Islamic Republic of Iran. 2019;33:64.

38. Holm C, Thomsen LL, Langhoff-Roos J. Intravenous iron isomaltoside treatment of women suffering from severe fatigue after postpartum hemorrhage. The Journal of Maternal-Fetal & Neonatal Medicine. 2019;32(17):2797-804.

39. Nguyen PH, DiGirolamo AM, Gonzalez-Casanova I, Pham H, Hao W, Nguyen H, et al. Impact of preconceptional micronutrient supplementation on maternal mental health during pregnancy and postpartum: results from a randomized controlled trial in Vietnam. BMC women's health. 2017;17(1):1-9.

40. Perelló M, Coloma J, Masoller N, Esteve J, Palacio M. Intravenous ferrous sucrose versus placebo in addition to oral iron therapy for the treatment of severe postpartum anaemia: a randomised controlled trial. BJOG: An International Journal of Obstetrics & Gynaecology. 2014;121(6):706-13.

41. Vaucher P, Druais P-L, Waldvogel S, Favrat B. Effect of iron supplementation on fatigue in nonanemic menstruating women with low ferritin: a randomized controlled trial. Cmaj. 2012;184(11):1247-54.

42. Nguyen PH, Grajeda R, Melgar P, Marcinkevage J, DiGirolamo AM, Flores R, et al. Micronutrient supplementation may reduce symptoms of depression in Guatemalan women. Archivos latinoamericanos de nutricion. 2009;59(3):278-86.

43. Gariballa S, Forster S. Effects of dietary supplements on depressive symptoms in older patients: a randomised double-blind placebo-controlled trial. Clinical nutrition. 2007;26(5):545-51.

44. Verdon F, Burnand B, Stubi CF, Bonard C, Graff M, Michaud A, et al. Iron supplementation for unexplained fatigue in non-anaemic women: double blind randomised placebo controlled trial. Bmj. 2003;326(7399):1124.

Appendixes

Appendix 1. Search strategy

CENTRAL search strategy:
#1 MeSH descriptor: [Iron] this term only
#2 MeSH descriptor: [Iron Compounds] this term only
#3 MeSH descriptor: [Ferric Compounds] this term only
#4 MeSH descriptor: [Ferrous Compounds] this term only
#5 MeSH descriptor: [Iron Supplement] this term only
#6 MeSH descriptor: [Ferrous supplement] this term only
#7 MeSH descriptor: [Ferric Compounds] this term only
#8 (iron or ferric* or ferrous)
#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#10 MeSH descriptor: [oral] this term only
#11 MeSH descriptor: [Injections, Intravenous] this term only
#12 (oral or intravenous or IV or inject)
#13 #11 or #12 or #10
#14 #9 and #13
#15 (depression or depressive or depressed)
#16 MeSH descriptor: [depression, depressive disorder] this term only and with qualifier(s): [Prevention & Control - PC]
#17 #15 or #16
#18#14 and #17
#19 MeSH descriptor: [Child] explode all trees
#20 MeSH descriptor: [Teenager] explode all trees
#21 kid* or junevile* or teenager* or child* or schoolchild*
#22 #19 or #20 or #21
#23#18 not #22

Pubmed Search strategy:
1. iron therapy/
2. iron derivative/
3. ferric/

4. ferrous/
5. (iron or ferric* or ferrous).ti,ab.
6. or/1-5
7. exp oral drug administration
8. exp intravenous drug administration/
9. (intravenous* or IV or inject*).tw.
10. or/7-9
11. 6 and 10
12. depression/
13. Depressive mood/pc [Prevention and Control]
14. (nonan?emi* or non an?emi* or NAID or IDNA).ab,ti.
15. ("depressive behavior" or "depressive affect" or "being epressed").ti,ab.
16. (depressive mood* or depressed patient*).ti,ab.

17. or/12-16
18. 10 and 17
19. exp Randomized Controlled Trial/
20. exp controlled clinical trial/
21. exp controlled study/
22. comparative study/
23. randomi?ed.ab,ti.
24. placebo.ab.
25. *Clinical Trial/
26. exp major clinical study/
27. randomly.ab.
28. (trial or study).ti.
29. 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28

Web of science search strategy:
#1 TS=("depression" OR "depressive mood" OR "depressive affect" OR "depressed patient")
#2 TS="depressive disorder"
#3 TS=(non-anemic OR non-anaemic)
#4 #1 OR #2 OR #3
#5 TS=(ferrous OR ferric OR iron)
#6 TS= (oral* OR intravenous* OR IV OR inject*)
#7 #4 AND #5 AND #6
#8 TS=((clinical OR control* OR placebo OR random OR randomised OR randomized OR randomly OR random order OR random sequence OR random allocation OR randomly allocated OR at random) SAME (trial* or group* or study or studies or placebo or controlled))
#9 #8 AND #7

#10 TS=HUMAN
#11 #10 AND #9

Clinicaltrials.gov search strategy:
Condition or disease = (depression OR depressive OR depressive mood OR depressive affect OR depressivee disorder OR depressive behavior OR hoplelessness) AND Other terms = iron AND (intravenous OR intravenous OR IV OR injection OR oral Or tablet)

WHO ICTRP search strategy:
(depression OR depressive OR depressive mood OR depressive affect OR depressivee disorder OR depressive behavior OR hoplelessness) = condition AND iron = intervention

Appendix 2. Cochrane risk-of-bias tool for quality assessment of the included studies

Ref	D1	D2	D3	D4	D5	D6	Quality
Calje, 2024	+	+	?	+	+	+	good
Kapoor, 2023	+	+	?	+	+	+	good
Tavcar, 2023	+	+	?	+	+	+	good
Vafa 2019	+	+	?	+	+	+	good
Holm, 2019	+	-	+	+	+	?	fair
Stewart, 2017	+	+	-	+	+	?	fair
Holm, 2017	+	-	+	+	+	?	fair
Sheikh, 2017	+	?	?	+	+	+	good
Nguyen, 2017	+	+	+	+	+	+	good
Perello, 2014	+	?	-	?	+	-	fair
Vaucher, 2012	+	?	+	+	+	+	good
Nguyen, 2009	?	?	?	-	-	-	fair
Gariballa, 2007	+	+	?	+	+	+	good
Verdon, 2003	+	+	+	+	+	+	good

D1, Risk of bias arising from the randomization process;
D2, Risk of bias due to deviations from the intended interventions (effect of assignment to intervention);
D3, Missing outcome data;
D4, Risk of bias in measurement of the outcome;
D5, Risk of bias in selection of the reported result;
D6, Overall risk of bias;
Low risk (+), High risk (-), Unclear (?);