Medical Science

To Cite:
Knap Z, Zielińska M, Iwański P, Kałużna J, Kraziński A, Mrowińska J, Mazur A, Grzywacz N, Chalimoniuk I, Hejman A. The Role of Selected Dietary Supplements (Vitamin D, Creatine, Folic Acid, and Omega-3 Fatty Acids) in the Management of Depressive Disorders: A Narrative Review. *Medical Science* 2026; 30: e186ms3972
doi: https://doi.org/10.54905/disssi.v30i175.e186ms3972

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Peer-Review History
Received: 18 April 2026
Reviewed & Revised: 30/April/2026 to 01/September/2026
Accepted: 07 September 2026
Published: 15 September 2026

Peer-review Method
External peer-review was done through double-blind method.

Medical Science
pISSN 2321–7359; eISSN 2321–7367

The Role of Selected Dietary Supplements (Vitamin D, Creatine, Folic Acid, and Omega-3 Fatty Acids) in the Management of Depressive Disorders: A Narrative Review

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ABSTRACT

Depression is one of the most disabling conditions in the world, and many patients do not achieve full remission with standard treatments. There has been increasing interest in dietary supplements as potential adjuncts to standard treatments for depression. This narrative review examines the evidence regarding vitamin D, creatine, folic acid and omega-3 fatty acids in depressive disorders, with a focus on their potential use alongside standard treatment. A search of PubMed and Google Scholar was performed to identify meta-analyses, systematic reviews and randomised controlled trials evaluating these supplements in the treatment of depression. All four supplements examined have been associated with reductions in depressive symptoms. Vitamin D and omega-3 fatty acids have shown benefits in people with depressive disorders, while folic acid may be beneficial as an adjunct to antidepressants in people with low folate levels. Creatine has also shown some benefits in people taking antidepressants or undergoing cognitive behavioural therapy, although results are not yet conclusive. These findings suggest that dietary supplements could play a role in the treatment of depression, albeit as an adjunct to antidepressant medication. Further studies are required to determine optimal dosing and treatment duration, as well as the patient populations most likely to benefit.

Keywords: Supplementation, vitamin D, creatine, folic acid, omega-3 fatty acids, depression, depressive symptoms

1. INTRODUCTION

Depression is one of the most common of all psychiatric disorders and poses a major problem for public health all over the world. It is marked by a sad mood, a

lack of interest or pleasure in activities and by other symptoms which have an effect on an individual's quality of life. Although pharmacological and psychological treatments work well for many people who have depression, there are some people for whom these treatments produce an inadequate response. Because of this, there has been a growing interest in complementary methods of treating depression. In recent years the study of nutritional psychiatry has attracted ever more attention because of the possibility that nutritional factors can affect brain function; for instance, various nutrients have been investigated for their potential to influence depression, such as those mentioned by Hoepner et al., (2021).

Vitamin D is one of the most researched supplements when it comes to mental health. Since the vitamin D receptor has been found in the central nervous system, vitamin D may play a role in the regulation of mood. Research into the effects of taking vitamin D supplements on depression has found that depression symptoms decrease as a result of such supplementation. Yet, because of the variety among these studies, the significance of the findings is questionable (Mikola et al., 2023; Ghaemi et al., 2024; Wang et al., 2024).

Creatine is another substance that has been looked at in connection with depression. It plays a role in the metabolic process of cells by producing ATP, a substance that is necessary for maintaining energy in the body's tissues, particularly in those organs and tissues which need a lot of energy to carry out their functions, such as the brain. Moreover, research studies have shown that creatine may have an antidepressant effect in people who have depression, particularly when it is used together with the treatments for depression that are currently prescribed to such patients (Kious et al., 2019; Pazini et al., 2019; Eckert et al., 2025).

The review looks at the evidence regarding the use of vitamin D, creatine, folic acid, and omega-3 fatty acids in the management of depressive disorders, with a focus on their mechanisms of action, clinical effectiveness, and the limitations of the current evidence.

A short summary of the present state of knowledge

Depression is usually best dealt with by using a multidisciplinary method, since pharmacotherapy and psychotherapy on their own are generally not enough to achieve full remission. Vitamin D, creatine, folic acid and omega-3 fatty acids have all become more popular as over-the-counter supplements, and this very fact makes it necessary to examine the evidence for their use in depression rather than just consider their availability. With respect to these four, the existing literature shows only modest or moderate benefits at most. Vitamin D and omega-3 fatty acids have the most substantial body of evidence; folic acid has mostly been studied as a supplement to antidepressant treatment; and creatine has the least advanced evidence of all.

2. REVIEW METHODS

A search for relevant literature was conducted on PubMed and Google Scholar. The search was conducted from January to March 2026 and covered English-language publications published between 2000 and 2026. The search strategy included combinations of the following keywords: “depression,” “depressive disorders,” “vitamin D,” “creatine,” “folic acid,” “folate,” and “omega-3 fatty acids.” The search included systematic reviews, meta-analyses, and randomised controlled trials which looked at the effects of these supplements on depressive symptoms or depressive disorders. Exclusion criteria included publications in languages other than English, lack of full-text availability, animal or in-vitro studies without direct clinical relevance, case reports and case series, and publications that did not provide information regarding depressive outcomes or the effects of the investigated supplementation.Publications that did not meet the pre-defined eligibility criteria were discarded. It was this final group of 24 publications that was included in the narrative synthesis. The article screening and selection process followed the principles of the PRISMA guidelines and is presented in the PRISMA flow diagram (Figure 1).

3. RESULTS AND DISCUSSION

Vitamin D and depressive symptoms

Although vitamin D is officially regarded as a vitamin, it acts more in the way of a prohormone since it is metabolically converted into its biologically active form, 1α,25-dihydroxycholecalciferol (calcitriol) (Ghaemi et al., 2024). Various physiological mechanisms have been suggested to account for its possible antidepressant effect, such as neuroprotection, immunomodulation, influences on cellular growth and differentiation, and anti-inflammatory activity which is in part due to reduced levels of C-reactive protein (CRP) (Gowda et al., 2015).

Meta-analysis entries in PubMed as a rule state that taking vitamin D reduces the severity of depressive symptoms, the extent of the effect however varying according to the dose, the length of treatment, and the features of the patients (Ghaemi et al., 2024; Mikola et al., 2023; Gowda et al., 2015; Wang et al., 2024). The advantage is greater among those who have a low level of 25-hydroxyvitamin D in

their blood at the start and in women (Mikola et al., 2023). That does not happen in all studies: a number of studies published around the same time found no antidepressant effect that was clinically significant (Menon et al., 2020). This discrepancy in the literature is one of the reasons why we should be cautious about considering the effectiveness of vitamin D as established.

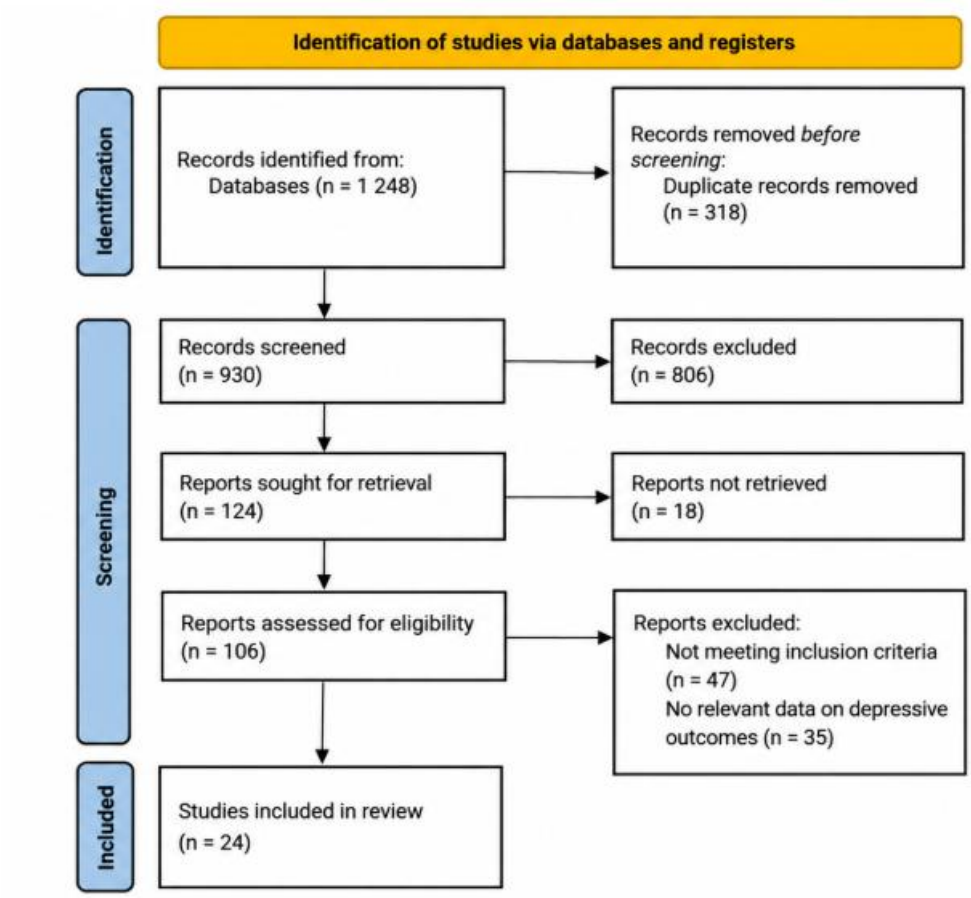

Figure 1. PRISMA flow diagram.

The degree of consistency in the dosing recommendations is even less. A meta-analysis showed that the greatest benefit was achieved at a dose of 8,000 IU each day when this dose was continued for at least eight weeks (Ghaemi et al., 2024). On the other hand, other studies have set a much lower efficacy threshold—about 2,000 IU per day (Mikola et al., 2023) or around 2,800 IU per day (Gowda et al., 2015; Wang et al., 2024)—eight weeks once again being the shortest duration linked with a benefit (Wang et al., 2024). The figures cannot be directly compared since the original studies differed in the patients' baseline 25(OH)D levels, the severity of their depression, the outcome measures used, and the length of follow-up, and none of the meta-analyses in question arrived at their estimates from a single, well-powered dose-ranging trial (Ghaemi et al., 2024; Mikola et al., 2023; Menon et al., 2020). We therefore consider the range of 2,000 to 8,000 IU per day to be only an approximate indication obtained from a variety of secondary sources, and not a validated dosing range. In keeping with this caution, several long-term randomised controlled trials which used a dose of 2,000 IU per day found that in people who did not have depressive symptoms at the beginning taking the supplement at that dose had no effect on preventing the development of depression, even though it may have been helpful when symptoms were already present (Mikola et al., 2023). The issue of efficacy must also be considered in relation to safety; the doses linked with the greatest reported benefit in the aforementioned literature—up to 8,000 IU per day—go beyond the tolerable upper intake level established for the average adult; continued intake above this level is known to carry a risk of hypercalcemia and hypercalciuria and would therefore require the monitoring of serum 25(OH)D and calcium levels. None of the meta-analyses mentioned above included systematic long-term safety data for the higher doses tested, which means that their findings regarding efficacy can only be translated into a practical clinical guideline to a limited extent.

When looking at all the existing literature, we do not think that there is a specific dosage of vitamin D which should be recommended for the treatment of depression. It should be up to the prescribing clinician to decide whether or not to give vitamin D supplements and at what dose, the clinician having to consider the patient's initial 25(OH)D level, any other disorders they may have, and the safety concerns already mentioned, rather than following a standard protocol when antidepressants are being used. Vitamin D supplementation should be regarded as an auxiliary measure, not as a treatment on its own. Creatine and its effect on depressive symptoms first gained popularity as a supplement within the fields of sports and exercise science, where it is employed in order to enhance muscle strength and performance. The present review, though, regards it as a nutraceutical which influences brain bioenergetics and may thus have an effect on depressive symptoms (Kious et al., 2019; Pazini et al., 2019; Dos Santos & Bittencourt, 2025). At the moment, the studies that are available have mostly tested it as an added treatment rather than as a treatment by itself. A recent meta-analysis (involving 1,093 participants) showed a statistically significant but only clinically small decrease in the severity of depressive symptoms as a result of taking creatine - although the authors considered the overall certainty of the evidence to be very low (Dos Santos & Bittencourt, 2025). The effect was more apparent in patients who had been diagnosed with a formal depressive disorder, but the sensitivity analyses carried out in that same meta-analysis indicated that the benefit might have been overestimated, a point which should be highlighted rather than ignored (Eckert et al., 2025).

In a trial that lasted eight weeks, the addition of creatine to cognitive behavioural therapy (CBT) led to a reduction in PHQ-9 scores that was about five points greater than that achieved with CBT alone (Kious et al., 2019). The results are less consistent in the case of treatment-resistant depression: small open-label studies in which creatine was added to SSRIs or SNRIs reported considerable improvement, while dose-finding randomised trials found no advantage over placebo (Pazini et al., 2019). With regard to bipolar depression, 6 g per day of creatine did not result in a significant improvement in MADRS scores when compared with placebo, even though the rate of remission was numerically higher in the creatine group (Dos Santos & Bittencourt, 2025).

Creatine and depressive symptoms

Preclinical studies and narrative reviews indicate that creatine increases the availability of phosphocreatine and ATP, improves mitochondrial function, and has an effect on serotonergic and dopaminergic transmission, neurogenesis, and neuroplasticity (Kious et al., 2019; Pazini et al., 2019; Dos Santos & Bittencourt, 2025). In animal models it reduced depression-like behaviour and enhanced the effects of SSRIs, a result which was mainly seen in female subjects (Kious et al., 2019). The tolerability in the different clinical studies was good and there was no obvious rise in adverse events when compared with placebo (Dos Santos & Bittencourt, 2025).Yet the body of evidence is limited. A number of the trials are small, in some the samples are highly selected (for instance, only women are included), and there is a great deal of methodological variety (Guzek et al., 2023; Dos Santos & Bittencourt, 2025). Overall, creatine appears to provide a small to moderate additional benefit when given together with SSRIs or CBT in adults with major depressive disorder, but the average effect size does not consistently reach clinical significance. With regard to bipolar disorder, any possible antidepressant benefit has to be balanced against the risk of triggering a hypomanic or manic episode. It is only through larger, more well-designed trials that efficacy, the optimal dosage, and long-term safety can be established.

Folic Acid and depressive symptoms

Folic acid and its related compounds—folate—is one of the micronutrients that has been most thoroughly investigated in relation to depression, mainly because of its important role in one-carbon metabolism, in the production of neurotransmitters, and in the regulation of homocysteine; homocysteine levels are frequently observed to be higher in depressed patients (Liwinski & Lang, 2023). Depressed people usually have lower folate levels than healthy individuals, and more recent evidence indicates that a low folate status is associated with a greater risk of developing depressive disorders (Gao et al., 2024; Liwinski & Lang, 2023). The mechanism involved is fairly well understood since folate is required for the synthesis of serotonin, dopamine, and norepinephrine as well as for methylation processes in the central nervous system, and deficiency has been linked to a poorer response to antidepressant treatment (Liwinski & Lang, 2023; Hoepner et al., 2021). The harder question to answer is whether folic acid actually results in an improvement of depressive symptoms, and in this instance the evidence is a bit more consistent than that for the other supplements looked at in this review. The meta-analyses from 2024 concluded that, folate supplementation greatly reduced the severity of symptoms, although it also pointed out considerable heterogeneity among the studies with regard to dosage, duration, and the form of folate used (Gao et al., 2024). A separate meta-analysis from 2022 of randomised trials also found significant improvements in both BDI and HAM-D scores (Khalili et al., 2023).

A systematic review and meta-analysis found that where folate is used in addition to SSRIs or SNRIs, there are significant improvements in HAM-D scores, together with higher rates of response and remission—this showing that folate is more effective when used as an augmentation strategy than when employed on its own (Altaf et al., 2021). Similarly, a more extensive review of nutritional interventions for mood disorders also reached the same conclusion: the benefits were most noticeable in cases where the patients already had a folate deficiency and when folate was added to standard antidepressant treatment, while the evidence for using folate as monotherapy was considerably weaker. Folic acid and its derivatives seem to be a fairly promising auxiliary treatment, in particular when patients have a proven folate deficiency and are already on antidepressant therapy. Nevertheless, the evidence for this is of only moderate methodological quality and moderate consistency and is therefore not strong; it is still necessary to carry out further large, well-designed randomised controlled trials if the efficacy is to be established, the optimal dosage determined, and its clinical role defined (Gao et al., 2024; Liwinski & Lang, 2023; Khalili et al., 2023; Altaf et al., 2021; Hoepner et al., 2021). The effect of omega-3 fatty acids on the symptoms of depression have for a long time been linked to a reduction in the severity of depressive symptoms, the effect being only small to moderate and the results differing from study to study (Kong et al., 2025; Lu et al., 2021). The evidence is strongest in relation to clinical depression; on the other hand, preventive trials carried out in the general population have not shown any significant benefit (Norouziasl et al., 2023; Okereke et al., 2021). Three separate syntheses all reach a broadly similar conclusion: a dose–response meta-analysis of 67 RCTs found that for each additional 1 g per day of omega-3s there was an improvement in symptoms, and this was more apparent in cases of established depression (Norouziasl et al., 2023); a meta-analysis of 36 RCTs reported a small but statistically significant overall effect (SMD −0.26) (Kong et al., 2025); and an umbrella review of 22 meta-analyses found that beneficial effects were seen in most of the individual analyses, even though several of the individual analyses did not reach statistical significance (Lu et al., 2023).

In a systematic review and meta-analysis involving about 2,300 participants with major depressive disorder, omega-3 supplementation was found to perform significantly better than a placebo (Hedges' g = −0.45), with the greatest improvements observed in cases of moderate-to-severe depression; the authors considered omega-3s mainly as an adjunctive treatment for patients who do not respond fully to standard antidepressants (Idowu et al., 2025). The details regarding dosage in this instance are more precise than those for vitamin D. The dosage range that is most strongly supported is 1–2 g/day, with EPA making up at least 60% of the formulation (Kelaiditis et al., 2023). According to dose–response modelling, the greatest benefit is seen around 1.5 g/day and a U-shaped curve is observed — higher doses did not result in any additional benefit (Norouziasl et al., 2023). In studies where the EPA content was limited to ≥60%, there was a significantly greater reduction in symptoms, whereas EPA doses above 2 g/day gave no extra advantage (Kelaiditis et al., 2023).

The most recent (2025) meta-analysis has also narrowed down the most favourable profile: mild to moderate depression, no previous use of pharmacotherapy, a dose of 1,000–1,500 mg/day for over eight weeks, and an EPA:DHA ratio between 1:1 and 2:1. Nevertheless, omega-3 supplementation has not consistently resulted in a better treatment response or higher remission rates when compared to a placebo (Kong et al., 2025); a positive outcome on a symptom-severity scale does not necessarily mean that more patients achieve remission.

Omega-3 fatty acids and depressive symptoms

The advantage of EPA can be explained in a mechanistic way. A 2021 review showed that in randomised controlled trials the antidepressant effects were consistently linked to formulations high in EPA rather than those high in DHA, indicating that changes in inflammatory pathways, the stabilisation of neuronal membranes, and alterations in lipid signalling might be involved—possibly due to differences in membrane incorporation, cytochrome P450–dependent lipid metabolism, and activation of CB2 receptors via endocannabinoid derivatives (Kalkman et al., 2021). A review from 2024 also mentioned neurotransmission and the modulation of neuroplasticity as additional possible mechanisms, but it pointed out that the results of the trials are still inconsistent and depend on dosage, the EPA:DHA ratio, and the patients' baseline characteristics (Serefko et al., 2024).

These conclusions are subject to several limitations. Most meta-analyses show a considerable degree of heterogeneity, together with possible publication bias, as well as meaningful differences regarding the populations studied, the length of the intervention, the composition of the supplement, and the outcome measures (Kong et al., 2025; Kelaiditis et al., 2023; Norouziasl et al., 2023). The VITAL-DEP trial provides a useful counterpoint in this regard: in older adults who did not have significant depressive symptoms at the beginning, long-term supplementation with omega-3 fatty acids did not prevent depression, and in fact the composite depression

outcome was very slightly higher in the omega-3 group, even though the scores on the mood scales were not significantly different (Okereke et al., 2021).

This finding suggests that the evidence for the use of omega-3 as an adjunctive treatment should not be extended to a preventive context. Omega-3 fatty acids—particularly those mainly found in EPA—appear to be a reasonable choice for individuals who are already suffering from a depressive disorder, even though the overall effect is only slight and therefore does not offer a solid justification for using them as a standalone treatment. Here, both the composition, the dose, and the particular characteristics of each patient seem to be more important than they are in the case of vitamin D, which is why the 1–2 g/day EPA-rich formulation should form the basis of clinical decision-making rather than be treated as a strict protocol. The main characteristics and findings of the studies included in this review are summarized in Table 1.

Table 1. Summary of clinical evidence on the effects of vitamin D, creatine, folic acid, and omega-3 fatty acids in depressive disorders.

Supplement	Study	Population (n)	Intervention / dosage	Main result
Vitamin D	Gowda et al., (2015)	Adults with depression (n = 948)	Vitamin D supplementation (various doses)	Reduction in depressive symptoms compared with placebo.
	Mikola et al., (2023)	Adults (n = 3,280)	Vitamin D supplementation (various doses)	Significant improvement in depressive symptoms, especially in individuals with low baseline 25(OH)D levels.
	Ghaemi et al., (2024)	Adults with depression (n = 1,153)	Vitamin D supplementation (dose–response analysis)	Dose–response relationship; greatest effect estimated at 8,000 IU/day.
	Wang et al., (2024)	Patients with primary depression (n = 1,012)	Vitamin D supplementation (varying doses)	Beneficial effect on depressive symptoms.
	Fu et al., (2024)	Older adults (n = 1,184)	Vitamin D supplementation (various doses)	Reduction in depressive symptoms in older patients.
Creatine	Kious et al., (2019)	Adults with depression (n = 52)	Creatine 5 g/day as adjunct to CBT (8 weeks)	Greater reduction in PHQ-9 scores compared with CBT alone.
	Pazini et al., (2019)	Patients with depression (n = 100)	Creatine 3–5 g/day as adjunct to antidepressants	Improvement in depressive symptoms, particularly in treatment-resistant depression.
	Eckert et al., (2025)	Adults with depressive symptoms (n = 1,093)	Creatine supplementation (1–10 g/day)	Statistically significant but clinically small reduction in depressive symptoms; very low certainty of evidence.
Folic acid / Folate	Altaf et al., (2021)	Patients with MDD (n = 1,212)	Folate (0.5–15 mg/day) as adjunct to SSRIs/SNRIs	Improved depressive symptoms, response and remission rates.
	Khalili et al., (2023)	Adults (n = 916)	Folic acid supplementation (various doses)	Significant improvement in depressive symptom scores.

	Gao et al., (2024)	Patients with depressive symptoms (n = 2,483)	Folate supplementation (various doses)	Beneficial effect on depressive symptoms, with substantial heterogeneity between studies.
Omega-3 fatty acids	Okereke et al., (2021)	Older adults without depression at baseline (n = 25,871)	Marine omega-3 fatty acids (1 g/day, long-term)	No significant effect on the prevention of depression.
	Kelaiditis et al., (2023)	Adults (n = 1,876)	Omega-3 supplementation (EPA-enriched formulations)	Greater reduction in depressive symptoms with EPA-enriched preparations.
	Norouziasl et al., (2023)	Adults with depression (n = 3,924)	Omega-3 supplementation (0.5–2 g/day)	Significant improvement in depressive symptoms, particularly in established depression.
	Kong et al., (2025)	Patients with depression (n = 4,283)	Omega-3 supplementation (various EPA/DHA ratios)	Small overall antidepressant effect; potentially optimal dose 1,000–1,500 mg/day.
	Idowu et al., (2025)	Adults with MDD (n = 1,406)	Omega-3 supplementation (various doses)	Significant reduction in depressive symptoms, especially in moderate-to-severe depression.

The possible benefit from taking vitamin D supplements appears to be greatest among people who have a vitamin D deficiency or who already suffer from a depressive disorder. There is at present no evidence to back up the use of vitamin D for the prevention of depression in the general population. Moreover, since the doses used differ so much, with some studies employing doses that nearly reach the accepted safety limits, this does not offer sufficient evidence to warrant the establishment of a standard dosing protocol. While the theory concerning creatine—namely, improved brain bioenergetics—is mechanistically sound, the clinical evidence in this instance is the weakest of the four and is based on small sample sizes, often with very strict selection criteria. Omega-3 fatty acids, particularly those high in EPA, show the most consistent dose–response relationship of all the supplements, although the average effect size is still small and does not apply to prevention. The strongest evidence for folic acid is in its use as an add-on to SSRIs or SNRIs in patients who have been shown to have a folate deficiency, with only much weaker support for its use in all other cases.

The findings of this review are broadly similar to those of earlier summaries, but they also indicate that the apparent benefit of taking nutritional supplements should not be assumed to apply to all patient groups. With regard to vitamin D, Ghaemi et al., (2024) observed a dose-response relationship for depressive symptoms, the largest estimated effect being seen at a dose of 8,000 IU per day, although the certainty of the evidence varied according to the outcome and the most significant effects were found in the shorter trials. On the other hand, the large VITAL-DEP trial showed that 2,000 IU per day had no preventive effect over a median period of 5.3 years in adults who did not have clinically significant depressive symptoms at the beginning of the study (Okereke et al., 2020). Taken together, these studies suggest that a distinction should be made between treating existing depressive symptoms and preventing depression in groups who are otherwise asymptomatic. Regarding creatine also differs. The most recent meta-analysis carried out by Eckert et al., (2025) covered 11 trials with 1,093 participants, but it rated the certainty of the evidence as very low and stated that the average effect was below the level usually regarded as clinically important on the Hamilton Depression Rating Scale. Even though a small randomised trial which added creatine to CBT produced promising results, the pilot nature of the study and its small sample size mean that the findings cannot be widely generalised. Earlier studies on bipolar depression had also not shown a significant difference between the groups in terms of MADRS change, even though there was a numerically higher rate of remission with creatine. Thus, it appears that creatine should be considered an investigational adjunct rather than an established treatment. As far as folate is concerned, the available evidence indicates that it plays a supportive role. Altaf et al., (2021) observed that when folate was used in conjunction

with treatment with an SSRI or an SNRI, there were improvements in HAM-D scores, response, and remission. Khalili et al., (2023) arrived at the same conclusions based on six randomised trials, even though they noted that the evidence was not enough to enable the formulation of clinical guidelines. The more recent umbrella meta-analysis by Gao et al., (2024) confirmed the signal but also highlighted differences concerning dose, duration, and the form of folate. Therefore, the evidence supports further research into folate augmentation, especially in patients with low folate levels, rather than suggesting it as monotherapy.-3 fatty acids shows the same kind of tension between effects that can be detected statistically and those that have real-world clinical value.

Norouziasl et al., (2023) found that taking omega-3 supplements resulted in an improvement in depressive symptoms, the largest estimated benefit being about 1.5 g per day for individuals who already had depression, while Kelaiditis et al., (2023) noticed greater effects when using formulations enriched with EPA at doses below 2 g per day. A meta-analysis published in 2025 revealed a small overall effect but found no significant increase in the rates of response or remission, substantial heterogeneity and publication bias still existing (Wang et al., 2025). In a similar way, an umbrella review concluded that several meta-analyses had reported significant benefits, although the effect sizes were generally small and heterogeneity was high (Lu et al., 2021). Thus, the findings suggest that omega-3 fatty acids might be used as a possible adjunct in some patients, but should not be used as a replacement for antidepressant treatment or as a general preventive measure. The total amount of existing literature supports the main interpretation presented in this review, namely that nutritional supplements could be of some use as adjunctive treatments, even though their effects vary considerably according to the group of people studied, the patients' initial nutritional state, the formulation used, the dose administered, and the length of the treatment. The apparent differences between the various supplements are therefore more likely to result from variations in how the patients were selected and in the design of the studies than from actual differences in biological effectiveness.

Future randomised trials should stratify the participants prospectively according to their baseline nutrient status and the severity of their depression and should use standardised formulations, clinically relevant outcomes, and a follow-up period long enough to determine which patient groups benefit in a meaningful way. The fact that these findings are linked has nothing to do with them all telling a similar story about effectiveness, but is instead because each of the studies suffers from the same evidence-related problems—namely, from having heterogeneous populations, inconsistent dosing protocols, different treatment durations, and a mix of outcome measures in the original studies. Because of this heterogeneity, we are not suggesting a general supplementation protocol here, as doing so would go beyond what the existing body of literature can support. It can only be confidently established what the optimal dosage, treatment duration, and target populations should be for any of the four supplements through the conduct of larger, adequately powered, and longer randomised controlled trials—preferably ones that have harmonised dosing and outcome measures.

4. CONCLUSION

The evidence currently available indicates that vitamin D, creatine, folic acid, and omega-3 fatty acids may offer only small advantages with respect to depressive symptoms when used in addition to conventional treatment, although the strength and consistency of this evidence vary considerably depending on the particular intervention. Vitamin D should be recommended mainly to people who have a deficiency or who are already suffering from depressive symptoms, whereas there is no justification for using it routinely as a means of preventing depression in the general population. Folate has the strongest case for being used as an augmentation approach when taken with antidepressants, especially in instances where folate levels are low. Omega-3 fatty acids, in particular those high in EPA, might provide a slight extra benefit in cases of existing depression, although no preventive effect has been observed. The evidence relating to creatine is still in its early stages and must be approached with caution because of the small number of participants, the diversity of the studies, and the very low certainty of the results. In general, the present evidence does not support replacing standard antidepressant treatment with any of these supplements or adopting a one-size-fits-all dosing approach. It is necessary to carry out further research in the form of larger, well-powered randomised trials that use standardised interventions and measure clinically significant outcomes if we are to determine which patients are most likely to benefit.

Acknowledgments

We thank all co-authors and institutional staff for their support during the preparation of this review.

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Informed consent
Not applicable.

Ethical approval
Not applicable. This article does not contain any studies with human participants or animals performed by any of the authors.

Funding
This research did not receive any external funding like specific grant from funding agencies in the public, commercial, or nonprofit sectors.

Conflict of interest
The authors declare that they have no conflicts of interest, competing financial interest or personal relationship that could have influenced the work reported in this paper.

Data and materials availability
All data associated with this study are present in the paper

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