REVIEW

Food supplements to complement brain functioning: the benefits of a combination of magnesium, folic acid, omega-3 fatty acids and vitamin E [version 1; peer review: 1 approved]

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v1 **First published:** 03 Feb 2022, **11**:140
https://doi.org/10.12688/f1000research.75856.1

Latest published: 03 Feb 2022, **11**:140
https://doi.org/10.12688/f1000research.75856.1

Abstract

Diet and nutrition play a fundamental role not only in human body composition and in physiology, but have also relevant effects on mood, mental well-being and cognitive performance. In particular, the preservation of mental well-being through a healthy lifestyle, including a well-balanced diet and, in case, through the intake of specific food supplements, is of particular relevance in the perspective of global human ageing, as the brain is affected significantly by a persistent presence of stress factors. Due to the increasing burden of mental and neurological disorders and to the universality of food as a modifiable risk factor, even limited improvements in nutritional habits may translate to a considerable rise of well-being and mental health in the global population. Moreover, the use of targeted, well-balanced food supplements aiming to support the mental health and well-being will probably represent a relevant tool in future decades, together with an increased awareness of the importance of nutrition, also considering the COVID-19 pandemic and the related stressful events and limitations we are still experiencing at global level. The aim of this review is to summarize the experimental and clinical data reported in the literature concerning the beneficial effects of a subset of micro- and macronutrients contained both in food and in supplements, namely magnesium, folic acid, docosahexaenoic acid, eicosapentaenoic acid, and alpha-tocopherol, on a series of disorders, including stress, anxiety, low sleep quality, and low cognitive performance.

Keywords

folic acid, eicosapentaenoic acid, alpha-tocopherol, docosahexaenoic acid, magnesium, mental well-being, food supplements, stress

Open Peer Review

Approval Status ✔

	1
version 1 03 Feb 2022	✔ view

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Author roles: Businaro R: Conceptualization, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: Editorial assistance was supported by an unconditioned grant from Angelini Pharma S.p.A., Rome, Italy.

Grant information: Editorial assistance was supported by an unconditioned grant from Angelini Pharma S.p.A., Rome, Italy.
The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

How to cite this article: Businaro R. **Food supplements to complement brain functioning: the benefits of a combination of magnesium, folic acid, omega-3 fatty acids and vitamin E [version 1; peer review: 1 approved]** F1000Research 2022, **11**:140 https://doi.org/10.12688/f1000research.75856.1

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Introduction

According to a definition of the World Health Organization (WHO), mental health is an integral and essential part of health, and is more than just the absence of mental disorders or disabilities. In 2018, the mental health has been defined as a condition of well-being where subjects realize their own abilities, can cope with the normal daily stress, work productively and can contribute to their community (https://www.who.int/news-room/fact-sheets/detail/mental-health-strengthening-our-response). Mental health is at the basis of our ability to interact with each other, think, emote, and poor mental health is associated, among others, with unhealthy lifestyle.

It is expected that the burden of mood-related disorders and stress-induced cognitive impairment will continue to rise globally in the next years. Changes in lifestyle induced by stress can cause overnutrition and reduced physical activity, possibly leading to obesity and metabolic syndrome; indeed stress is known as one of the main inducers of obesity development and visceral fat, that in turn underlie a faster aging process.[1] Alterations in energy expenditure balance disrupt the crosstalk between metabolism and immune system, causing the activation of an immune response and the development of a systemic inflammation with a low-grade, which is one of the main risk factors for the development of depression as well as cognitive impairment.[2] According to Straub *et al.,*[3] neuroendocrine pathways are implicated in the regulation of energy: inflammation induces higher levels of cortisol in the serum, by stimulating the hypothalamic-pituitary-adrenal axis (HPA) and the sympathetic nervous system (SNS), leading to a sickness behavior, with a marked reduction of gut, muscle and brain activity. The elevated levels of proinflammatory cytokines observed in systemic inflammation target brain cells binding to specific cytokine receptors expressed on glial cells and neurons thereby directly affecting the brain function, increasing the risk to develop depression. A prolonged exposure to cytokines with a proinflammatory activity impairs synaptic plasticity, contributing to mood alterations as well as to cognitive disorders.[4]

According to WHO, neurological and mental disorders, as well as substance abuse will represent 10% of the global burden of disease and 30% of burden of non-fatal disease (https://www.who.int/news-room/facts-in-pictures/detail/mental-health). On this basis, the protection, restoration and promotion of mental health can be considered a vital concern of subjects, and of worldwide societies and communities. There is a strong need for actions in promotion of mental health to improve psychological well-being (https://www.who.int/news-room/fact-sheets/detail/mental-health-strengthening-our-response).

This narrative review aims to summarize the experimental and clinical data reported in the literature concerning the beneficial effects of a subset of micro- and macronutrients, namely magnesium, folic acid, docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and alpha-tocopherol, on a series of disorders, including stress, anxiety, low sleep quality, and low cognitive performance.

The role of nutrition in mental health and well-being

Brain function, structure and composition are linked to the intake and availability of appropriate micro- and macronutrients, as most essential minerals and vitamins are not produced by the body and should be taken through food. Genetic conditions, medical therapies, inadequate food intake, and systemic diseases can lead to deficiencies of particular nutrients.[5] The impact on brain function of food intake and quality makes the diet a modifiable variable to target mental health, mood and cognitive performance. For example, vitamins and minerals play key roles in the body, *e.g.* in signal transduction or as cofactors in a number of enzymatic reactions. Nutritional excess or deficiencies of some minerals and vitamins can deeply affect the peripheral and central nervous systems from the early development to the adulthood.[5] The composition of the diet directly affects also endogenous neuropeptides, neurotransmitters, gut hormones, and the gut microbiota.[6,7]

During the last years, there has been a greater number of epidemiological studies analyzing the link between mental condition and dietary patterns. Longitudinal and cross-sectional studies revealed that the adoption of a Western diet or a diet based on highly processed food proportionally increases the risk of development of psychiatric symptoms, such as anxiety and depression. Conversely, the adoption of a Mediterranean-style diet increased the protection from the development of a mental disorder.[8,9]

In several studies, the onset of psychiatric symptoms has been shown to be preceded by a particular dietary pattern. Among them, "SMILES", a single-blind, parallel-group, 12-week, randomized controlled trial, revealed remarkable effects after 3 months of a dietary intervention on depression of moderate-to-severe grade, with a greater improvement of symptomatology and remission achieved in 32% of participants in the intervention study group.[10] The beneficial effects of the Mediterranean-style diet on depression have been confirmed by more recent randomized controlled trials, including the HELFIMED trial (where the Mediterranean-style diet was supplemented with fish oil)[11] and the PREDI_DEP trial (where the Mediterranean-style diet was supplemented with extra-virgin olive oil).[12] In contrast, supplementation with multi-nutrients in the randomized controlled trial MooDFOOD did not affect the persistence of major depression in subclinical and overweight depressed subjects.[13] A study performed on the data of adult subjects from the 9-year follow-up of the Depression and Anxiety Netherlands Study showed a dose-response association between the severity of chronic depression or anxiety disorders and a poorer diet quality in all study participants.[14] Overall, the recent findings from clinical trials seem to support the use of a complex of care measures including first line pharmacological and psychological treatments, as well as lifestyle interventions (*e.g.* improvement of diet quality, addressing smoking cessation, increase of physical activity) may have a greater effect on depression.[15] With reference to sleep disorders, and in particular to insomnia, a study has been recently performed on nursing university students to determine the prevalence of sleep disorders and to evaluate in which way eating habits, health status, lifestyle and students' performance are related to daytime and night-time symptoms of interrupted sleep. The InSOMNIA study revealed a high prevalence of sleep disturbances associated with low adherence to Mediterranean diet.[16] The compliance with a Mediterranean-style diet has been associated with lower risk for insomnia and better sleep quality in other recent studies not only in young students, but also in older adults, without gender differences[17] and either toward indirect effects or a direct effect on health through a weight improvement.[18]

Many complex mechanisms are at the basis of the impact of nutrition on the brain and on mental well-being. Recent research has focused in particular on the hippocampus, a region of the brain associated with creativity, memory, learning and mood. The physiological process of aging includes structural changes in the brain where the pattern and rate of hippocampal atrophy is responsible for cognitive impairment and mood disorders often observed in the elderly. An annual 0.2% loss in total brain volume begins in subjects from the age of 35 years.[19] The intake of omega-3 polyunsaturated fatty acids (PUFAs) and fish consumption may affect brain morphology changes, as suggested by a randomized controlled trial testing the omega-3 PUFA supplementation in mild cognitively impaired subjects and in cognitively intact individuals. The trials showed that the memory domain of cognitive functions was positively affected by PUFA supplementation.[20] The hippocampus is especially modulated by dietary patterns, possibly due to its metabolism and its ability to undergo neurogenesis also during adulthood, well beyond the gestational period. The hippocampus neurogenesis is related to mood and cognition. Consequently, dietary intervention on hippocampal neurogenesis modulation has been considered as a target or a tool able to affect mental health, as well as brain function and plasticity.[21] Data supporting the link between nutrition and adult hippocampal neurogenesis are increasingly emerging from studies in animal models. Among others, a recent study demonstrated that intermittent fasting can have a neuroprotective effect through the activation of different signaling pathways, and that a murine model fasted intermittently shows increased hippocampal neurogenesis *versus* sedentary mice fed an ad libitum diet.[22] Rats fed a diet rich of saturated fats and refined sugar experienced insulin resistance and decreased neurogenesis and neuronal plasticity, together with issues in memory and learning.[23,24] Finally, a novel study involving a group of preadolescent children revealed a negative association between sugar intake and the performance in Torrance Test of Creative Thinking, while dietary fiber intake was positively associated with results obtained in this creativity standardized test, where the hippocampus is known to be involved.[25]

Gut microbiota and mental health: a well-established relationship

The microbiota, can be defined as the totality of bacteria, archaea, fungi, viruses, and protozoa that inhabits an organism as commensal microorganisms, and represents a unique fingerprint that characterize every subject, with a marked variability, depending on geographical area, diet, and use of antibiotics and other drugs.[26] The gut microbiota, a biomass of up to 2 kg in adult humans, has a vital role in human health: it is able to break down dietary fibers and other food components that we cannot digest, produces vitamins, stimulates the immune system maturation, and prevents the gut colonization by pathogenic species.[27] Among others, gut microbiota can produce or stimulate the release of several substances that can reach the brain through the circulation and cross the blood–brain barrier (BBB). Evidence has highlighted a key role for microbiota as a link between the gut and essential brain processes, such as microglial activation, neurogenesis and myelination, involved in cognition, mood and behavior, as recently reviewed elsewhere.[28] Gut microbes can influence T and B lymphocytes in the wall of the gut, with consequences on the release of pro-inflammatory cytokines that in turn can increase the BBB permeability.[29] The vagus nerve represents another route from the gut to the brain.[27]

An approach based on the experimental manipulation of gut microbiota across natal and adult environments is leading to a better comprehension of the interplay between cognitive variation and the gut microbial community. In this setting, studies in murine models showed that the maternal gut microbiome can affect the neurodevelopment during key prenatal periods, without any environmental challenge, through the release in maternal serum of microbiota-dependent metabolites.[30] Faecal microbiota transplant (FMT) from donor mice of different age to young adult mice revealed the detrimental effect of FMT from aged donors on central nervous system, thus supporting the relevance of the gut-brain axis in ageing and providing a basis to test therapies targeting the microbiota in elderly subjects to improve their cognitive functions.[31] A fine-tuning of the brain-gut axis has been highlighted also in humans by the recent findings of a link between brain behavior and development in the offspring and the composition of maternal prenatal gut microbiota.[32]

Moreover, patients with an imbalance in function and composition,[27] *i.e.* a range of psychiatric and neurological disorders exhibit *versus* healthy controls of gut microbiota.[33] In turn, diseases, as well as disease-associated factors, such as drug intake or a very different diet, can influence the composition of gut microbiota.[27]

A high-quality diet may be of support in the modulation of gut microbiota at short- and long-term, reduce brain inflammation and stress and subsequently preserve a good cognitive function. Dietary factors can directly shape the gut microbiota composition in both rodents and humans.[6] A meta-analysis including gut microbiota studies highlighted the unique effects of the Mediterranean diet on intestinal microbiota.[34] However, dietary patterns may affect not only the gut microbiota but also the intestinal permeability, and in turn affect the mental health. In more detail, an increased permeability induced, among others, by a high-fat diet, may allow the activation of the immune cells in the intestinal wall by the lipopolysaccharides produced by bacteria, finally leading to a higher systemic inflammation.[35]

In addition to a high-quality diet, the use of prebiotics and probiotics and of specific food supplements (*e.g.* alpha-tocopherol) could be helpful to modify the gut microbiota and restore a healthy status.[26,36] In the context of mental health, some placebo-controlled studies in humans have reported effects of probiotics on emotion- and stress-related parameters. Among others, a double-blind, randomized, placebo-controlled clinical trial on patients with a diagnosis of major depressive disorder showed that the administration of probiotic supplements for 8 weeks led to an improvement of mood, in addition to a decrease of insulin levels and of high-sensitivity C-reactive protein in the serum.[37] More recently, the administration for 24 weeks of tablets containing heat-inactivated *Lactobacillus gasseri* CP2305 to healthy subjects under stressful conditions led to an improvement of sleep quality, mental state, and gut microbiota.[38] A larger number of studies and of greater size is required to further support a direct effect of probiotics on brain function, possibly with greater standardization of strains, doses, and measure of study outcomes.[27] Finally, a special class of probiotics, the psychobiotics, has been recently defined based on their ability to produce or stimulate the production of neurotransmitters, enteroendocrine hormones and other molecules, with a large range of applications, including mood and stress alleviation.[39] A beneficial role for probiotics in mitigating anti-depressive effects, both as an adjunct to antidepressant drugs or as a stand-alone intervention, has been recently suggested elsewhere.[40] This is of course an interesting field with huge potentialities; however, the administration of psychobiotics in the general population should be carefully evaluated and supported by more evidence.

The burden of mental health disorders in general population

Several disorders, such as anxiety, stress, sleep disturbance, can affect both the mental well-being and the physical health. Stress can be defined as a reaction of the body to the impairment of a condition of equilibrium and is a common problem in several societies, where there are different types of pressures.[41] Stress can prolong the release by adrenal glands of the steroid hormone cortisol and to subsequent effects on immune cells and on the production of free radicals.[42] When in excess, the free radicals reduce the antioxidant stock in our body, leading to a damage of molecular and cellular components, and leading to oxidative imbalance and inflammation.[43] Stress can contribute to a reduction of the quality of life (QoL) and lead to a final state of exhaustion, possibly implying cardiovascular diseases, skin problems, hypertension, infertility, inflammatory bowel syndrome and diabetes mellitus, among others.[41] Unhealthy eating habits may result in an increased level in stress; in more detail, improper nutritional balance, insufficient vitamin intake, and excess consumption can exacerbate the stress response and create an imbalance of stress hormones.[41] The Mediterranean diet, based on higher intake of fruit, vegetables, nuts, whole grain, seeds, beans, and higher levels of fibers, and on lower levels of red meat, is protective against inflammation and stress. Stress increases the metabolism and creates a greater physiological demand that can be supported through a supplementation with minerals and vitamins. Stress protection is also conferred by omega-3 fatty acids.[41]

Sleep disorders, such as obstructive sleep apnea and insomnia, can cause an impairment of the circadian rhythm. They can be particularly frequent and relevant in aged subjects, where sleep quality, particularly self-reported sleep quality, and QoL are strictly correlated.[44] Sleep has a restorative effect on the endocrine and the immune system, supports the recovery of the nervous system and has a fundamental role in memory, learning and in synaptic plasticity.[45] Adequate sleep is fundamental for the preservation of metabolic equilibrium. Disturbances and short duration of the sleep are risk factors for inflammation, that is associated with a higher risk of cardiovascular diseases, such as hypertension,[46] metabolic disorders, overweight and obesity.[47] Of interest, a recent cross-sectional observational study of 13-15 years old subjects revealed that sleep duration and timing seem to be independently associated with weight status in adolescence, and consequently may be important targets to prevent obesity.[48] The HPA may be an important mediator of the effects of sleep disorders on general health and well-being. Cortisol is the main hormone of the HPA axis, and is characterized by circadian rhythmicity.[47] Pineal melatonin affects the regulation of the HPA axis mentioned above and displays a dynamic circadian rhythm as well, as it is produced at night from 5-hydroxytryptophan and its production is blocked by intense light.[49] A positive association between adequate sleep and a health-related lifestyle, including the choice of a healthy dietary pattern, has been shown in subjects of different age. Different studies showed that subjects who sleep less tend to prefer high-energy foods, with a lower intake of vegetables. But ingested food can affect sleep quantity and quality as well. In particular, foods affecting the availability of the essential amino acid tryptophan, as well as the biosynthesis of melatonin and serotonin, may be the most beneficial in sleep induction.[50]

Anxiety can be defined as an emotion characterized by worried thoughts, tension, and physical symptoms, such as rapid heartbeat, higher blood pressure, sweating, dizziness, in the absence of an immediate threat. Anxiety can occur occasionally in healthy individuals, but it becomes pathological if disproportionate and persistent. The estimated global prevalence rate of anxiety disorders is currently about 28%.[51] Anxiety and depressive disorders are associated with increased inflammatory activity, HPA-axis hyperactivity, and an increased tone of the autonomic nervous system.[52] Knowledge about the main roles of bioelements in anxiety disorders increased in the latest years.[53] In more detail, deficiency of some elements can lead to an excessive release of glutamate and to excessive activation of the HPA axis. Conversely, the regulatory function of bioelements in the body can possibly lead to anxiolytic-like effects, by virtue of their ability to modulate neurotransmission, as well reviewed elsewhere.[54] Of interest, a cross-sectional study has recently highlighted that increased intake of micronutrients acting as methyl donors was related to a reduced probabilities of psychological disorders, as better described below.[55] These data were confirmed by another cross-sectional study, showing an inverse relationship between anxiety and dietary intake of B vitamins, with the dietary intake of biotin associated with a lower risk of stress and anxiety only in female subjects.[56]

Low cognitive performance, including low concentration, learning, memory and reasoning, may be due to fatigue, tiredness, stress. An optimal cognitive performance is fundamental during all stages of life. During childhood, the cognitive performance is critical to optimize brain development, while during adulthood it is important to maintain a good cognitive functioning. Finally, during aging, it is of primary importance to delay the cognitive decline, considered as a phase of transition between healthy aging and dementia.[57] A healthy diet, rich in PUFAs, polyphenols and other nutritional supplements, such as vitamins, can be beneficial for cognitive performance.[6]

The global prevalence of common mental health disorders among adults has been examined fundamentally by two studies: the first one, published by Steel *et al.* in 2014, estimated a lifetime prevalence of 9.6% for mood disorders, 29.1% for all mental disorders, 12.9% for anxiety, and 3.4% for substance abuse.[58] The second study estimated a global prevalence of anxiety and depression of 3.6% and 4.4% respectively, with a greater prevalence in female subjects *versus* male subjects (https://apps.who.int/iris/bitstream/handle/10665/254610/WHO-MSD-MER-2017.2-eng.pdf).

The global prevalence of the mental health disorders described above in the general population has shown a dramatic increase with the recent COVID-19 pandemic, as highlighted by a systematic review and meta-analysis including participants from about 30 Countries. In more detail, the global prevalence estimate following the COVID-19 outbreak was 26.9% for anxiety, 36.5% for stress, 28.0% for depression, 50.0% for psychological distress, 24.1% for post-traumatic stress symptoms and 27.6% for sleep disorders.[59]

The omega-3 fatty acids role in mental health and well-being

Dietary fats or lipids are not only a main source of energy, but play a role also in several other processes, *e.g.* as components of cell membranes, regulators of enzymatic activity, precursors of bioactive molecules, regulators of gene expression. Fatty acids are classified on the basis of the number of double bonds in their molecules; among them, PUFAs have ≥2 double bonds, mostly in the *cis* configuration. PUFAs consist of 3 fatty acids: DHA, alpha- linoleic acid (ALA) and EPA. The human body can synthetize the n-3 PUFAs EPA and DHA from ALA through a series of desaturation, elongation and β-oxidation reactions occurring first in the endoplasmatic reticulum and then in the peroxisomes of animal tissues. ALA is considered an essential fatty acid (EFA) as it is not synthetized by the body.[60] ALA is found in some vegetables, while DHA and EPA are abundant in fish, cultivated marine algae and human milk. Foods enriched with n-3 PUFAs and supplements are also available as DHA and EPA source.[60]

About 20% of the dry weight of the brain and 1/3 of all fats in the central nervous system are composed by omega-3 PUFAs; they maintain membrane fluidity for synaptic signaling process, regulate neuronal membrane excitability, improve memory and learning.[61]

The adequate daily intake for DHA and EPA for adults is 250-500 mg, based on cardiovascular risk considerations.[60]

Omega-3 PUFAs EPA and DHA have both independent and shared effects on the brain, and represent a potential treatment for several neurodegenerative and neurological disorders by virtue of their neuroprotective properties.[62] DHA is the most abundant n-3 PUFA in the brain and is part of the structural lipids in cell membranes, in particular of

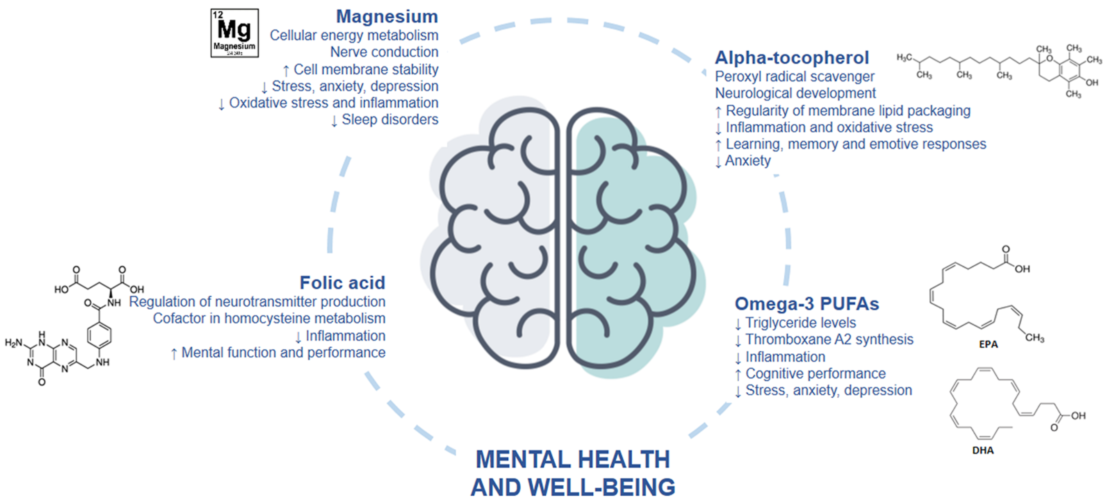

Figure 1. Main effects of omega-3 fatty acids EPA and DHA, magnesium, folic acid and vitamin E in mental well-being. (↓): downregulation; (↑): upregulation.

phospholipids in the retina and in the nervous tissue, with a major role in maintenance of neuronal membranes, in maintenance of normal brain functions and in cognitive process (Figure 1).[62] DHA and EPA can be converted in their respective endocannabinoid derivatives, docosahexaenoyl-ethanolamine and eicosapentaenoyl-ethanolamine, showing possible antidepressive effects.[63] In addition, specialized proresolving mediators, such as protectins, resolvins, lipoxins, and maresins, are bioactive lipids derived from omega-3 PUFAs produced by innate immune cells. This class of lipids counteracts oxidative stress and inflammation promoting the resolution of inflammation.[64] DHA and EPA blood levels can be affected both by genetic polymorphisms and by gender.[62,65]

Based on current literature, it has been established that DHA supports a healthy brain development as one of its building blocks and supports the nerve transmission; DHA also may support the working memory, concentration levels and the brain performance in aging adults.[66] The developing brain accumulates large amounts of DHA, in particular during the first years of life; it is acquired mainly from the mother through the placental transfer in the pre-natal period and though the breast milk post-natally. However, the brain increases its capacity to synthesize DHA in parallel with gestational age.[67] Studies in murine models submitted to psychological stress revealed the important role of a balanced diet in supporting brain development for later cognitive function. In more detail, the studies showed an improvement in cognitive behaviors, memory and plasticity markers in the brain of adolescence in rats fed a diet enriched with the omega-3 PUFAs, EPA, DHA, and vitamin A. Of interest, the protective effect of the PUFA-enriched diet were preserved during adulthood, long after the termination of the exposure to a stressful environment.[68] A very recent study confirmed the positive role of dietary DHA on the preservation of cognitive function also in aged rats fed a processed foods diet.[69]

Moving to data derived from observational studies and trials in humans, an inverse correlation between plasma levels of EPA, DHA and total omega-3 PUFAs and cognitive impairment, dementia risk and depressive symptoms in the elderly has been highlighted in several studies.[19,62,70–72] It has also been suggested that an adequate dietary intake of omega-3 PUFAs can slow the age-related mild cognitive impairment (MCI) and protect against the risk of dementia.[73] Literature data also indicate that the impact of stress can be limited by an adequate amount of DHA in the brain.[73] Matura *et al.* (2021)[74] investigated the relationship in cognitively healthy individuals between cognitive performance, dietary fat composition and brain morphology, showing that a high ratio between saturated fatty acids and (n-3) PUFAs has a significant correlation with lower grey matter volumes and poorer verbal memory performance in areas of the left prefrontal cortex, a region involved in memory processes, thus suggesting that a diet rich in PUFAs could positively affect the morphology in brain areas important for executive functions and memory. A trial on healthy volunteers revealed that the Zone diet and omega-3 PUFAs were able to increase well-being and to modulate the mood state, as revealed by ad-hoc questionnaires. The supplementation with omega-3 PUFAs was related to an increase of vigor and a decrease of negative factors such as angry, anxious and depressive mood in healthy subjects.[75] Several other trials supported the effectiveness of a PUFA-enriched diet on the preservation of cognitive functions in the elderly.[76]

Of interest, some studies indicated that an inter-individual variability in omega-3 PUFA clinical response seems to be related to genetic variants, especially in APOE4 carriers,[77] and to epigenetic modifications of genes involved in PUFA metabolism and associated with the risk of mental disorders, such as autism spectrum disorders and attention deficit/ hyperactivity disorder,[78,79] thus supporting an approach based on subject stratification, as indicated by the emerging "precision nutrition" concept.

The magnesium role in mental health and well-being

Magnesium is an essential ion to the human body, as it is the second most abundant intracellular cation after potassium, with a daily reference intake of 375 mg.[80] In more detail, the Recommended Dietary Allowance (RDA) for magnesium is 400–420 mg for male subjects and 310–320 mg for female subjects with age >19 years (https://ods.od.nih.gov/factsheets/Magnesium-HealthProfessional/). Magnesium acts as a physiological calcium antagonist, and is involved in hundreds of enzymatic reactions, including those related to protein synthesis and energy metabolism, DNA stability and DNA repair as well as the preservation of the electrical potential of nerve tissue and cell membranes. Magnesium contributes to normal electrolyte balance and to the normal function of the nervous system, as well as to the reduction of fatigue and tiredness, particularly in situations of inadequate micronutrient status, and its reserve tends to be exhausted by our body in times of increased stress, so it is fundamental to ensure a proper intake of this mineral (Figure 1).[81]

Reduced magnesium levels have been associated to migraine, depression, epilepsy. It regulates N-Methyl-D-aspartate (NMDA) excitability, so that in magnesium deficiency NMDA receptors become hyperexcitable and this condition can be further amplified by the inhibitory action of gamma-aminobutyric acid (GABA) receptors, which are regulated by magnesium. Several authors hypothesized that magnesium may relieve depression by blocking NMDA receptors that are involved in depression development.[82] Moreover, it has been shown that magnesium plays anti-inflammatory and anti-depressant effects.[83,84] Interestingly, a magnesium uptake leads to a decrease in body weight and a loss of fat mass which is accompanied by a decrease in serum inflammatory parameters. There is a bidirectional relationship between obesity and depression as the first is characterized by a chronic inflammation of low-grade, with involvement of the stress axis. Obesity can increase by 55% the risk of comorbid depression, that in turn leads to a 58% increased risk of obesity.[85] Clinical studies have shown that hypomagnesemia correlates with the severity of depressive symptoms[86] and with the onset of metabolic syndrome and diabetes often associated with obesity conditions. Magnesium deficiency affects energy metabolism and may stimulate the onset of inflammation-associated metabolic disorders, particularly in obese patients. In addition, hypomagnesemia may increase oxidative stress by acting on the activities of antioxidant enzymes such as glutathione, catalase and superoxide dismutase. Magnesium was shown to enhance synaptic plasticity by inducing increased levels of presynaptic synapsin 1, PSD93 and PSD95. Magnesium exerts an anti-inflammatory activity through the regulation of the NF-kB/Nrf2 signaling pathways.[87] Magnesium supplementation was able to improve memory and learning in patients affected by dementia and in healthy animals and was shown to play a key role in neuronal maturation.[88]

The relationship between magnesium concentration in the serum and mental health has been highlighted in a cross-sectional study that showed an association between low magnesium concentration in the serum and greater perceived stress in healthy women without psychiatric disorders.[89] Consistently, magnesium supplementation has been shown to be beneficial in stress alleviation in a phase IV, investigator-blinded trial enrolling healthy subjects with severe/extremely severe stress and low magnesemia and randomized 1:1 to magnesium–vitamin B6 combination or magnesium alone and treated accordingly for 8 weeks.[90] Other studies showed a positive effect of magnesium supplementation on biomarkers and symptoms of stress and on sleep disorders. In a double-blind, randomized trial on healthy elderly subjects, magnesium supplementation improved subjective measures of insomnia, and, likewise, insomnia objective measures, such as concentration of serum cortisol, renin and melatonin.[91] A very recent systematic review and meta-analysis of 3 randomized control trials comparing oral magnesium to placebo in older adults in 3 different Countries did not led to statistically significant data, but however it supported the use of oral magnesium supplements for insomnia symptoms.[92] The authors suggested the need for additional well-designed clinical trials due to the substandard quality of currently available studies.

The role of alpha-tocopherol in mental health and well-being

Plant-derived alpha-tocopherol is one of the eight isoforms of vitamin E. It increases the regularity of lipid packaging in cell membranes and is part of the antioxidant defense system, functioning physiologically as a chain-breaking antioxidant that protects polyunsaturated fatty acids from peroxidation (Figure 1).[93] The reference alpha-tocopherol daily dietary intake for adult subjects is 12 mg.[94] Major dietary vitamin E sources, are fortified ready-to-eat cereals; greens such as spinach; nuts, seeds; and vegetable oils, in particular safflower and sunflower.[94] Vitamin E can be stored in the fatty tissue, and is located mainly within the cell membranes, where it protects against lipid peroxidation, a consequence of oxidative stress, counteracting reactive oxygen species formation. Alpha-tocopherol is involved in the inhibition of free radicals production, whereas gamma-tocopherol neutralizes the free radicals already present.[95]

Studies focusing on alpha-tocopherol deficiency involving humans or animal models established the critical role of this molecule in protecting the central nervous system, and in particular the cerebellum, from motor coordination deficits and oxidative damage. Emerging data also demonstrate the critical roles of alpha-tocopherol in preserving memory, emotive responses and learning, as reviewed elsewhere.[96]

Several studies in animal models supported a positive role for alpha-tocopherol in preservation of cognitive function and sleep quality. Among others, a preclinical study in a murine model showed the neuroprotective effect of vitamin E on memory impairment induced by chronic sleep deprivation.[97] In addition, a chronic treatment of old rats with alpha-tocopherol significantly increased in a dose- and/or time-dependent manner the synthesis rate and the levels of monoaminergic neurotransmitters (noradrenaline, dopamine, serotonin) in striatum and in hippocampus, both involved in motor coordination and memory processing.[98] Moving to humans, a study involving 124 young male subjects showed a significant association between self-reported poor sleep quality and low intakes of some nutrients, including alpha-tocopherol.[99] These findings are in agreement with the association between sleep regulation and oxidative stress suggested by previous reports,[100] based on the hypothesis that the antioxidant properties of alpha-tocopherol could improve the quality of the sleep. However, additional investigations are necessary to explore the potential beneficial effect of alpha-tocopherol on sleep quality. A meta-analysis evaluating the association between intakes of the most common 3 antioxidants (β-carotene, vitamin C, vitamin E) and the risk of Alzheimer's disease revealed that the intake of the 3 antioxidants is able to reduce the risk of Alzheimer's disease, and that vitamin E exhibits the most relevant protective effect.[101] In addition, serum alpha-tocopherol resulted to be significantly correlated with cognitive function in a population of older subjects.[102] However, these findings have not been confirmed by other studies,[103] including the Ginkgo Evaluation of Memory observational study, based on a large older population, where plasma antioxidants, including alpha-tocopherol, were not significantly related to future risk of dementia, Alzheimer's disease or cognitive decline before dementia diagnosis.[104]

The synergistic effect of vitamin E administered together with omega-3 PUFAs has been related to the complementation of the anti-oxidant and anti-inflammatory activity exhibited by the two different classes of compounds. It is well known that oxidative stress is one of the main inducers of neural cell damage and death in neurodegenerative diseases.[105]

The CARES Trial 1 evaluated the role of a specific nutritional protocol to improve the cognitive performance in subjects affected by MCI. Preliminary results were encouraging and showed improved performance in episodic memory and global cognitions in MCI patients, who have been following a diet enriched with omega-3 PUFAs and vitamin E for 12 months.[106]

Interestingly, a recent study suggested that the levels of circulating alpha-tocopherol do not provide a complete insight in vitamin E antioxidant capacity and activity. Special attention in observational and efficacy studies should be devoted not only to alpha-tocopherol plasma concentration, but also to its metabolism, marked by α-carboxymethyl-hydroxychroman and α-tocopheronolactone hydroquinone levels in the urine, as potential reflection of lipid oxidation.[107] Moreover, discrepancies among study results could be due to confounding factors or to different methods for antioxidant measurement in the body. In light of these considerations, additional trials are needed, with a special focus on redox potential of alpha-tocopherol in the setting of cognitive impairment and on preclinical phases of disease, with the enrollment in studies of younger populations.

The folic acid role in mental health and well-being

Vitamin B9, also known as folate, is a water-soluble vitamin, abundant in the liver and in vegetables and whose chemical structure include a pteridine ring, p-aminobenzoic acid, and gamma-linked glutamate residues. Daily reference intake for folate is 200 µg. Folic acid is the oxidized monoglutamate synthetic form of folate, quite rare in nature.[108] Both folic acid and folate must be metabolized to the metabolically active form L-methylfolate through a multi-steps process to play their roles. L-methylfolate can cross the BBB and regulate the production of the neurotransmitters serotonin, norepinephrine and dopamine, thus contributing to mental function and performance.[109] Folic acid is essential for the production and maintenance of new cells, RNA and DNA nucleotide synthesis, and consequently for cell division. Folic acid is also essential for the remethylation of homocysteine, acting as a coenzyme for one-carbon metabolism (Figure 1).[108] Folate plays a key role in the methionine cycle, which is involved both in the conversion of homocysteine to methionine and in the production of S-adenosylmethionine, a universal donor of the methyl group.[110] Elevated homocysteine levels have been linked to atrophy of the cerebral cortex and loss of magnesium: both of these effects can be reversed by vitamins B.[111–113]

Folic acid is necessary for mental function and performance, playing a role in learning, memory and reasoning, concentration, and resistance to stress,[114] and its deficiency is linked to the development of forgetfulness in mild form and irritability.[110] A relevant contribution to the comprehension of the role of folic acid during development came from the examination of the effects of folic acid deficient or replete diets in mice, containing either normal folic acid intake or no source of folate.[115] Folic acid deficient mice exhibited a significant impairment of memory *versus* control mice, associated with significant gene expression changes specific to the hippocampus. Folic acid supplementation alleviated the cognitive decline related to age and inhibited the apoptosis of neurocytes in a murine model of accelerated senescence, and the mechanism potentially involved could be the alleviation of telomere attrition,[116] since telomere length shortening has been related to MCI and Alzheimer's disease development.[117] However, data on the effect of folic acid supplementation on cognitive performance in humans are contrasting. Among them, Bryan *et al.* investigated the effects of a supplementation for 35 days with folate, vitamin B12, vitamin B6 or with placebo in healthy women included in a wide age range.[118] In addition, they examined the association between dietary intake of these vitamins and mood and cognition. Supplementation induced a positive effect on some measures of memory performance, but not on mood. Dietary intake status was associated with verbal ability, recall and recognition and speed of processing.[118] Conversely, a randomized controlled trial enrolling elderly people with elevated homocysteine levels treated for two years with vitamin B12 and folic acid did not experience any beneficial effect on cognitive performance.[119] Similar results have been obtained in another randomized clinical trial enrolling older MCI patients with high levels of homocysteine and supplemented for two years with methylcobalamin and folic acid. However, in this study the supplement led to a significant, even if not sustained, reduction in depressive symptoms at month 12.[120] Of interest, a cross-sectional study showed that a moderate folic acid intake was associated with lower ratios of depressions in a general population.[56] Finally, dietary methyl donor micronutrients intake (choline, folate, betaine, B6 and B12 vitamins methionine) was linked to reduced odds of psychological disorders, in particular in women and obese or overweight subjects.[55]

Food supplements for mental health and well-being

As reported above, stress is a common problem and induces greater physiological demands: more oxygen, circulation, energy, and consequently more metabolic cofactors are necessary.[1,41] Among others, the psychosocial stress experienced by subjects is particularly difficult to prevent. Nutritional interventions could confer resilience and rescue stress vulnerability, as reviewed above and elsewhere.[121] Moreover, according to recent clinical observations, specific nutrients could be helpful also in complex neuropsychiatric conditions, such as major depressive syndrome, bipolar disorders, and obsessive-compulsive disorder, among others.[122]

The dietary patterns leading to positive and protective effects against stress and inflammation are consistent with the Mediterranean diet characteristics described above.[9,123] Stress reduction is also supported by supplementation of minerals and vitamins. Additional stress protection is provided by the intake of omega-3 PUFAs.[41]

Deficiencies of micro- and macronutrients can be due to, among others, insufficient intake, concomitant diseases, aging, drugs, lifestyle, metabolic disorders and genetic alterations, and can lead to different outcomes. The relative lack of omega-3 PUFAs in the Western diet can lead to insufficient DHA in brain cell membranes. An insufficient omega-3 PUFA dietary supply may be particularly relevant during aging as studies in murine models revealed that the aging brain tend to lose DHA. The specific decrease of DHA in aged brain may be due to an age-associated reduction of some enzymatic activities, specifically involved in the incorporation of DHA into brain phospholipids. This process can be prevented through dietary supplementation of DHA, as shown in aged rats.[73]

For what concerns magnesium, hypomagnesemia can be genetically determined or be consequent to the use of certain types of drugs or to alcohol abuse, or can follow gastrointestinal loss or dysregulation of renal reabsorption in critically ill patients.[82] Magnesium deficiency always includes secondary electrolyte disturbances.[124] Alpha-tocopherol deficiency because of inadequate intake of vitamin E is not common and can occur more frequently in children than in adults, in the setting of chronic fat malabsorption or because of genetic abnormalities in hepatic alpha-tocopherol transfer protein or in lipoprotein synthesis. The development of clinical evidence of vitamin E deficiency can take several years of exposure to extremely low vitamin E levels and can impair the immune function, increase adverse events during pregnancy and distorts the carefully programmed development of the nervous system, leading to defects also in several developing organs.[125] Low folate intake or an anomalous folate metabolism as well as a deficiency of vitamin B12 or B6 induce homocysteine elevation, and hyperhomocysteinemia has been linked to a higher risk of cerebrovascular and cardiovascular disorders.[126] In addition, folate deficiency impairs DNA replication and cell division, with negative effects in particular on proliferating tissues, such as bone marrow.[110] Specifically-designed food supplements could represent a useful tool to limit the impact of disorders such as anxiety, stress, sleep disturbance, and help to preserve the cognitive function throughout life without the side effects of drugs. Currently marketed food supplements whose ingredients include the micro- and macronutrients folic acid, magnesium, PUFAs and alpha-tocopherol, are listed in Table 1. Among them, Libretto® appears of particular interest, as a single capsule fulfills the 100% of the recommended daily reference intake of folic acid according to Reg. (EU) n. 1169/2011, the 29% of magnesium and the 21% of vitamin E recommended daily reference intake, respectively (Table 2). Food supplements specific for memory loss, Alzheimer's disease and MCI

Table 1. An overview of currently marketed food supplements aimed at supporting mental well-being and brain function and containing different combinations of the ingredients omega-3 fatty acids, magnesium, folic acid and vitamin E.

	Libretto	Dr. Bohm energie complex	Neurofil	MorEpa	Moller's omega-3	Eye Q	Omega-3 mood	Moode
Product description	Food supplement with fish oil, vitamin E, magnesium and folic acid to support brain function	Food supplement to support stress situations/mental and physical activity	Food supplement formulated with omega-3 fatty acids, magnesium, folic acid, vitamins	A highly concentrated (85%) omega-3 food supplement that contributes rapidly to a balanced omega-3 index	A pure Norwegian cod liver oil, a combination of natural omega-3 and natural vitamins	A mix of high-quality fish oil (with the omega-3 fatty acids) and pure evening primrose oil (with GLA and other omega-6 fatty acids)	Food supplement to support emotional/brain health	A supporting product to antidepressant therapy. Through the balance between essential fatty acids, physical, psychic, and behavioral improvements can be achieved
Ingredients	Omega-3 fatty acids (EPA, DHA) Magnesium Folic Acid Vitamin E	Mate extract Schisandra extract Caffeine Co-enzyme Thiamine (B1) Vitamin B6 Vitamin B12 Folic acid Vitamin C Vitamin E Vitamin D3 Iron Zinc Selenium Chromium Copper Manganese	Omega-3 fatty acids (DHA, EPA) Magnesium Vitamin E Vitamin B12 Folic acid	Deep-sea fish oil concentrate Omega-3 fatty acids (EPA, DHA, other omega-3 fatty Acids)	Vitamin D Vitamin A Vitamin E Omega-3 fatty acids (EPA, DHA)	Omega-3 fish oil (EPA, DHA) Evening primrose oil (omega 6) (GLA) Vitamin E	Fish oil from 5 different sources (EPA, DHA) Vitamin E	Fish oil (EPA)
Daily intake	Children up to 6 years old: 1 capsule daily. Children/adolescents above 6 years of age and adults: 1-2 capsules daily.	1 coated tablet	1-2 capsules with water/meals	1 softgel with a meal	once per day 1 dessert spoon (5 ml)	6 capsules per day, divided into 2-3 intakes with meals (starting dose, first 12 weeks). 2-4 capsules per day (maintenance dose)	2 softgels with a meal	1-2 capsules, at the main courses

Table 2. Nutritional information of the novel food supplement Libretto®.

Average amounts	For 1 capsule	%NRV* for 1 capsule
Omega-3 Nutrients	620 mg	\
Of which:		
- **EPA - Eicosapentaenoic Acid**	375 mg	\
- **DHA - Docosahexaenoic Acid**	147 mg	\
Magnesium	110 mg	29%
Folic Acid	200 μg	100%
Vitamin E (d-Alpha Tocopherol)	2.5 mg	21%

A single capsule fulfills the 100% of the recommended daily reference intake of folic acid according to Reg. (EU) n. 1169/201, while it covers 29% of magnesium and 21% of vitamin E recommended daily reference intake, respectively.
NRV: Nutrient reference value.
*NRV daily reference intakes for vitamins and minerals (adults) according to Reg. (EU) n° 1169/2011.

have been marketed as well in the latest years as adjunct of therapies to compensate possible nutrient deficiencies, and their efficacy has been evaluated in several meta-analyses, with different results.[122]

Conclusions

The micro- and macronutrients folic acid, magnesium, alpha-tocopherol and the omega-3 PUFAs EPA and DHA play individual and shared neuroprotective effects in mental health and brain aging. Unfortunately, existing studies to inform dietary recommendations for patients with mood, anxiety or sleep disorders are often limited by study size, heterogeneous patients' populations, and poor methodology. Well-designed observational studies or clinical trials will be of major relevance in the field of diet and dietary supplements for mental health and well-being.

The future development in the field of mental health and nutrition will probably combine psychological and psychiatric research with neuroscience and nutritional genomics. The growing application of the emerging concept of "precision nutrition", *i.e.* a subject stratification based not only on genetics but also on other variables, such as the profiling of microbiota, physical activity, smoking habits, concurrent medications and other features, will probably increase the ability of dietary interventions to improve mental health and well-being. Considering the increasing burden of mental and neurological disorders and considering that food is a universally modifiable risk factor, even small improvements in nutritional habits could lead to large improvements in mental health and well-being in the global population, while improving the sustainability of healthcare systems by reducing the costs associated with cognitive decline and poor mental health. In addition to increased awareness of the importance of nutrition and to consequent improvement of nutritional habits, the growing development and use of targeted, well-balanced food supplements aiming to support the mental health and well-being will probably represent another relevant tool in future decades.

Data availability

No data are associated with this article.

Acknowledgments

Amalia Forte, *Ph.D.*, provided the medical writing support on behalf of Menthalia S.r.l., Naples, Italy.

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Open Peer Review

Current Peer Review Status: ✔

Version 1

Reviewer Report 11 July 2022

https://doi.org/10.5256/f1000research.79784.r142179

✔ **Ned D Heindel**
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This is an interesting, well written and timely article focused on the fundamental role of diet/nutrition on brain function. The importance of improved nutritional habits is also discussed, specifically the beneficial effects of micro- and macronutrients in food and supplements.

Some clarifications on the following would improve the manuscript.

- Please add rationale for the focus only on magnesium, folic acid, docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and alpha-tocopherol.
- A short discussion on the impact of the gut microbiome on brain metabolome would be interesting.
- Is there any evidence that other free fatty acids besides omega 3 influence brain function and well being?
- Is magnesium the only ion known to impact cognitive responses?

Is the topic of the review discussed comprehensively in the context of the current literature?
Yes

Are all factual statements correct and adequately supported by citations?
Yes

Is the review written in accessible language?
Yes

Are the conclusions drawn appropriate in the context of the current research literature?

Yes

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.