

# Nutrition and dietary supplements in psychiatric diseases

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## Abstract

Modern approaches to management of medical conditions are based on a holistic view, taking into account bidirectional connections between physical and mental health. The current pharmacologically focused model has so far provided modest benefits in addressing the burden of poor mental health. Convincing data suggest that diet quality and select nutrient-based supplements might influence a range of neurochemical modulatory activities, improving the management of mental disorders. Examples of these nutrient-based supplements include omega-3 fatty acids, S-adenosyl methionine, N-acetyl cysteine, zinc, B vitamins (including folic acid), and vitamin D. The traditional Mediterranean diet is considered to be the most beneficial diet in our region. Based on the results of preclinical studies, we are increasingly aware of the role of intestinal microbiota in the pathogenesis and potential treatment of mental disorders. Bidirectional signalling between the brain and the gut microbiome involving vagal neurocrine and endocrine signalling mechanisms influences mental and physical wellbeing. These findings suggest that using prebiotics, probiotics or in the strict sense psychobiotics, as well as incorporating fermented foods in the diet, could have a potential role in the management of mental disorders. As of now, we lack sufficient evidence to implement recommendations for dietary supplements in treatment guidelines, however, this might change in light of emerging data from contemporary research studies, at least for certain indications.

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## 1. Introduction

Physical and mental health are closely connected (1). Pharmacological treatment has only moderately reduced the burden of mental disorders. Recently, there has been extensive research on new treatment and prevention modalities for mental disorders (2). Nutritional psychiatry is a science that investigates the association between nutrition and mental disorders, an issue that was either

neglected or addressed in poorly designed studies (3). Although the determinants of mental health are complex and multi-layered, the studies have hitherto identified nutrition as an important factor in the development of mental disorders. Nutrition has long been known to play a role in the development of some cardiovascular, endocrine and gastrointestinal diseases (2). There is an old

saying that »there is no health without mental health«. The recent evidence suggests that good physical health and aerobic exercise are crucially important to good mental health (4). People with mental diseases have a higher rate of chronic low-grade inflammation, oxidative stress, impaired metabolism, alterations to intestinal microbiota and numerous other changes that can be mediated by nutrition (4). Overeating and the resulting obesity carry an increased risk for physical problems and poor mental health. Many mental disorders are associated with changed dietary patterns. These can be further mediated by some pharmacological agents responsible for weight gain and obesity, and thereby for the accumulation of mental health problems (5).

Unlike the modern Western dietary patterns, the traditional dietary models, such as the Mediterranean and Japanese diets, include a high intake of fruit, vegetables, fish, seafood, whole grain cereals and fibres, and relatively small amounts of dairy products and meat (6). The Mediterranean dietary model recommends regular exercise and adequate fluid intake, and allows drinking one to two glasses of (red) wine a day (7,8).

An increasing number of studies have pointed to the connection between gut microorganisms – microbiota – and the immune system, intestinal endocrine and nervous systems, and to the bidirectional communication between the gastrointestinal tract and the brain, often referred to as the gut-brain axis (9,10). The enteric nervous system is linked to the central nervous system via the vagus nerve and other nervous connections. Biologically active food compounds, products of the gut microbial metabolism and some molecules secreted by intestinal cells (enterocytes, enterochromaffin cells) and cells of the intestinal immune system are in-

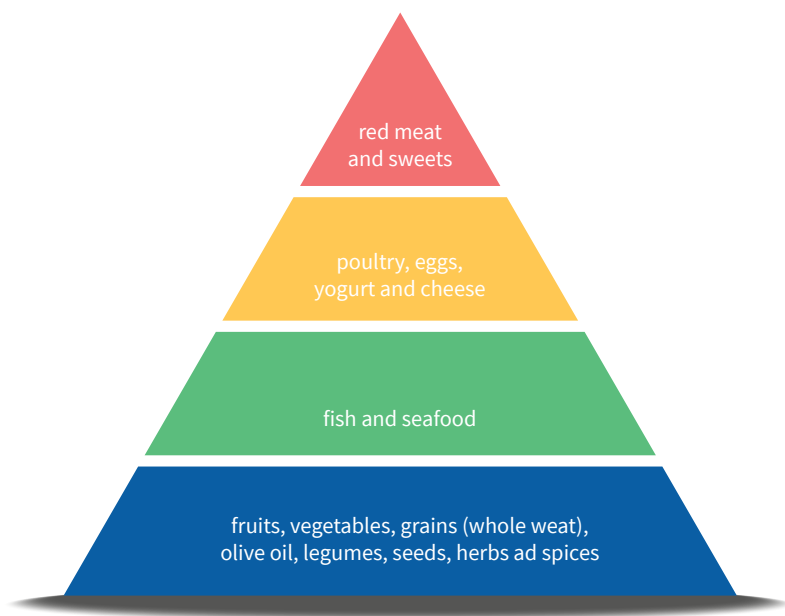
involved in neuron transmission along the gut-brain axis (11). Anti-inflammatory and pro-inflammatory cytokines and serotonin affect sleep, appetite and cognition (12). Prebiotics, probiotics and essential nutrients play an important role in the maintenance of healthy intestinal microbiota. The Western diet, rich in saturated fat, may have a negative impact on gut microbiota and may increase intestinal permeability and blood brain barrier leakage (4).

## 2. Effects of nutrition and dietary supplements

The consumption of increasingly processed and nutritionally poor food is on the rise, and as a result more and more people are overnourished and undernourished at the same time (2). Increased energy intake along with low intake of some important micronutrients and fibres may lead to shortage of nutrients important for the brain (2).

Normal high-level brain metabolism depends on amino acids, fats, vitamins, minerals and trace elements (4). Cigarette smoking, excessive alcohol use and lack of exercise are factors contributing to poor mental health. (2).

As shown by a Spanish study, eating a Mediterranean diet is associated with better mental and physical health (13). Dietary patterns during pregnancy and in early childhood have impact on mental health in adulthood (14,15). Prenatal exposure to acute food shortage during critical developmental periods is associated with higher incidence of affective and psychotic disorders and addiction in later life (16-18). Two systematic reviews of the studies investigating the relationship between nutrition and mental health have been published. They describe the association between unhealthy



**Figure 1:** Simplified Mediterranean Diet Pyramid

(adapted from »Oldways Mediterranean Diet Pyramid« (accessible on <https://oldwayspt.org/history-mediterranean-diet-pyramid>)

diet and depression and poor mental health in children and adolescents (19,20).

Epidemiological and prospective studies have pointed to the relationship between healthy dietary patterns and lower risk for depression (21,22), and suicide (23). Meta-analyses showed that adhering to the Mediterranean diet is associated with lower risk for mild cognitive impairment and Alzheimer's disease (24,25). The extensive PREDIMED randomised trial found that adhering to the Mediterranean diet with addition of nuts was inversely associated with the risk of depression, the effects of the diet being particularly beneficial in patients with type 2 diabetes (26). A clinical study showed that counseling to assist patients in the modification of their dietary patterns can be as effective as psychotherapy (27).

Dietary supplements with scientific evidence-based neurochemical modulation that have potential for treating mental disorders include: omega-3 fatty acids, S-adenosyl methionine, N-acetyl

cysteine, zinc, B vitamins and vitamin D (2). Focusing just on dietary supplements (28) may mask a potential role of nutrient combinations that meet the organism's natural physiological requirements (29). This can be illustrated by the intake of zinc: both preclinical and clinical studies have shown a relationship between zinc supplementation and better outcomes in patients with depression. Taking a zinc supplement was associated with a better response to antidepressant therapy (30,31). A combined action of omega-3 fatty acids and zinc was found to affect the epigenetic regulation of neuronal cells (32). Two studies on human neuronal cells showed that histones play a key role in epigenetic changes mediated by zinc and omega-3 fatty acids (32,33). Zinc reduced histone acetylation while omega-3 fatty acids improved the imbalance of acetylation homeostasis (32).

Ancient practice of subjecting foods to fermentation is one of traditional protective dietary patterns (3). Fermentation is a process of decomposition induced by microorganisms and enzymes of plant or animal origin. It has been used for preserving foods for more than a thousand years (34). The use of microorganisms from fermented foods seems to have beneficial effects on healthy intestinal ecosystem (3,34). Fermentation may improve bioavailability of B vitamins, magnesium and zinc (35-38). Proteolysis in fermented milk results in increased levels of peptides and free amino acids (39). In the field of psychiatry there is a paucity of clinical studies exploring the effects of fermented foods on mental health. One of these studies showed that in young adults which showed high neuroticism increased consumption of fermented foods was associated with fewer symptoms of social anxiety (40). Basic and animal studies describe be-

neficial effects of fermented nutrition on cognitive function and its neuroprotective mechanisms (41). Hypothetically, fermentation modifies chemical composition of nutrients, improves their effectiveness and bioavailability (42) and confers beneficial effects on gut microbiota composition (3).

### 3. Omega-3 polyunsaturated fatty acids

Dry weight of human brain comprises 80 % of lipids. Essential fatty acids enter the human organism exclusively with foods and make up 15–30 % of dry weight of the brain. They regulate cell signalling mechanisms via noradrenaline, dopamine and serotonin neuronal pathways. Also, they produce anti-inflammatory and anti-apoptotic effects and increase membrane fluidity and neurogenesis by enhancing brain-derived neurotrophic factors (BDNF) (2,43,44). Omega-3 fatty acids appear to have a role in preventing the onset of psychosis in high risk individuals (44,45). The results of meta-analyses, however, failed to provide firm evidence of the efficacy of omega-3 fatty acids in the treatment of schizophrenia (46–49). They confirmed, however, the benefits of omega-3 fatty acids for the treatment of depression symptoms, especially when given at high doses in combination with antidepressants (50,51). Studies of the treatment of bipolar disorders showed that omega-3 fatty acid supplementation was effective in reducing depressive symptoms, but had no effects on the symptoms of mania (52,53). Two meta-analyses showed small to moderate positive effects of high-dose omega-3 fatty acids in the treatment of children with attention-deficit/hyperactivity disorder (ADHD) (54,55). The third meta-analysis came to a similar conclusion, yet it pointed to diffe-

rences in methodology, strong placebo effect and evidence of bias which limited the objectivity of these findings (56). Omega-3 fatty acids are considered safe and well tolerated when given at doses of 5 g/day (44).

### 4. S-adenosyl methionine (SAM)

SAM is an endogenous sulphur-containing substance involved in methylation of neurotransmitters that regulate mood (2). Clinical research showed that SAM has a potential antidepressant efficacy (57) and can be used as an adjunct to antidepressants (58).

### 5. N-acetylcysteine (NAC)

NAC is used as the antidote for acetaminophen overdose (59). This amino acid compound affects glutamate and dopamine systems and has anti-inflammatory, antioxidative and neuroprotective effects (59,69). NAC was investigated for its potential in treating bipolar depression, schizophrenia, autism, trichotillomania and other compulsive and addictive behaviours. Yet, a systematic review of the literature showed that the results of these studies were inconclusive and that the use of NAC in psychiatry cannot yet be recommended (59,61).

Preliminary positive results need to be substantiated further with studies involving larger sample sizes and longer follow-up periods. Given its high tolerability and wide availability, NAC remains an important target of psychiatric research (62).

### 6. Elements

Zinc is present in the organism as a trace element. It regulates cytokines and hippocampal neurogenesis thro-

ugh BDNF stimulation, and affects N-methyl-D-aspartate and glutamate activity. In addition, it is involved in the metabolism of omega-3 and other essential fatty acids (63,64). Zinc deficiency has been associated with several depressive syndromes (65). Systematic review and meta-analysis of the literature showed that zinc supplementation, either alone or as an adjunct to antidepressants, is efficacious in the treatment of depression (30,31,63).

Research showed that children with ADHD and sleep disturbances (especially restless leg syndrome) tend to suffer from iron deficiency. Iron deficiency is thought to decrease the efficacy of psychostimulant medication (66). According to current guidelines, treatment of ADHD with iron supplements is indicated only in iron deficiency (67).

## 7. Vitamins

B vitamins are necessary for normal neuronal activity. Folate (vitamin B<sub>9</sub>) is essential to noradrenalin, serotonin and dopamine synthesis. Folate deficiency is frequently associated with depression and poor response to antidepressant therapy (68). The results of meta-analysis suggest that a short-term use of folate and vitamin B<sub>12</sub> does not improve depressive symptoms in patients treated with antidepressants, while prolonged therapy with vitamin B<sub>12</sub> may reduce the risk of relapse and prevent the onset of significant symptoms of depression in individuals at risk (69). As shown by a systematic review of studies, high-dose pyridoxin (vitamin B<sub>6</sub>) appears to have beneficial effects on extrapyramidal symptoms in patients treated with antipsychotics (70), yet the exact mechanism of these effects has not yet been clarified (71).

Systematic review of the literature showed no association between vitamin B<sub>12</sub> levels and cognitive decline or Alzheimer's dementia (72). There is no firm evidence either to support the efficacy of using vitamin A, vitamin C or vitamin E, alone or in combination with other antioxidants, for the prevention of cognitive decline (73).

Vitamin D is a neurosteroid involved in cell proliferation, differentiation and calcium signalling in the central nervous system, and is known for its neurotrophic and neuroprotective actions (74). Meta-analysis found no direct relationship between vitamin D supplementation and better depression treatment outcomes (75). Although decreased levels of vitamin D have been documented in patients with schizophrenia, there have been no clinical studies to date to investigate potential psychotropic effects of vitamin D supplementation in psychotic patients (76,77).

Psychiatric diseases may lead to vitamin and mineral deficiencies. It is well-known that alcoholics are at risk of thiamine (vitamin B<sub>1</sub>) deficiency, therefore supplementation of this vitamin may play an important role in the management of withdrawal symptoms. Although vitamin deficiencies are rare in the developed world, syndromes induced by these deficiencies, such as pernicious anemia or Wernicke's encephalopathy, should be considered in individuals with mental disorders (5).

## 8. Gut microbiota and psychobiotics

Human intestine comprises approximately 10<sup>14</sup>–10<sup>15</sup> microorganisms with more than 1,000 different species of bacteria (in addition to fungi, viruses and archaea) and outnumber human cells 10 to one. Gut microbiota has a key role in

intestinal metabolism, as well as in protection against environmental pathogens, in gut peristalsis and in immune responsiveness. These commensal bacteria can produce short-chain fatty acids and some neurotransmitters and essential amino acids, such as tryptophan. Through neuroendocrine mechanisms intestinal microbiota may regulate neurotransmitter levels in the brain, thereby affecting behaviour and emotional and cognitive processes of the individual. Vice versa, the brain can influence the microbiota composition (78,79). After birth, microbiota develops gradually and its ultimate composition largely depends on several factors, such as dietary patterns, diseases and treatment with antibiotics. Increasing awareness of the significant role of microbiota in physiological processes and of its impact on health has led to the formulation of various strategies targeting the composition and activity of gut microbiota. Over the past decades there has been a substantial increase in the use of probiotics – specific live microorganisms with beneficial effects on human health when administered in adequate quantity, and prebiotics – nondigestible food ingredients selectively stimulating the growth/activity of a limited number of beneficial bacteria. Their efficacy depends on several mechanisms, such as changes in gut microbiome, effects on gut mucosal barrier and immune system regulation (79). The microbiota-gut-brain axis has a potential role in the pathogenesis of several inflammation-related diseases, including mood disturbances, autism spectrum disorders, ADHD and obesity (80).

Psychobiotics are live bacteria which, when ingested in adequate amounts, confer brain benefits in patients with mental disorders (81). These bacteria can produce and secrete neuroactive compounds (GABA and serotonin) that act on

the brain-gut axis by inhibiting activity of the hypothalamic-pituitary-adrenal stress axis, or exhibit anti-inflammatory effects influencing the course of neuropsychiatric diseases (81). Some gut bacteria (*Lactobacillus acidophilus*, *Bifidobacterium infantis*, *Bifidobacterium longum*, *Candida* and *Streptococcus*) may produce psychotropic effects by secreting neurotransmitters, such as GABA, glycine, serotonin and catecholamine, or by impacting the endocannabinoid system (82). Psychobiotics have been investigated mainly in animal models, while clinical research is scarce. Meta-analysis of investigations involving patients with irritable bowel syndrome showed that the use of psychobiotics in individual clinical studies was associated with reduction in anxiety, depression and bowel inflammation (12). Healthy individuals who were taking a probiotic formulation consisting of *L.helveticus* and *B.longum* on a daily basis reported less psychological stress (83). Studies investigating the relationship between gut microbiome and depression did not give uniform results (84). A review of research on autism spectrum disorders showed that antibiotic and probiotic interventions improved behaviour and social communication in children with autism (85). Currently, there is a lack of clinical randomised and placebo-controlled studies that would clearly support the efficacy of probiotics in maintaining good mental health (86-88).

## 9. Conclusion

The relationship between nutrition, microbiota, gut metabolism, immune system and autonomic and central nervous systems is a frequently addressed issue. The basic-level findings that are currently available are limited to the recognition of the mechanisms of action.

There is a lack of relevant research that would provide evidence-based guidelines for clinical use. However, based on the findings obtained so far, nutritional therapy and the use of dietary supplements have the potential to advance the prevention and treatment of mental disorders.

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