Review Article

Nutritional Aspects of Depression in Adolescents - A Systematic Review

Abstract

Depression is defined as a cluster of specific symptoms with associated impairment affecting 7.4% of the adolescents globally. As part of the systematic review, around 1000 relevant articles published between January 1978 and December 2017 were identified by systematic online search from 6 electronic databases (PubMed, PsycInfo, Science Direct, MEDLINE, Scopus, and Google Scholar) and overall, 56 relevant studies were included in the current review as per the inclusion criteria. Findings highlight the potential importance of the relationship between healthy dietary patterns or quality and positive mental health throughout life span. Various nutrition and dietary compounds have been suggested to be involved in the onset maintenance and severity of depressive symptoms and disorders. Nutritional compounds might modulate depression associated biomarkers. In this context, several healthy foods such as olive oil, fish, nuts, legumes, dairy products, fruits, and vegetables have been inversely associated with the risk of depression and might also improve symptoms. In contrast western dietary patterns including the consumption of sweetened beverages, fried foods, processed meats, baked products have been shown to be associated with an increased risk of depression in longitudinal studies. Diet and nutrition offer key modifiable targets for the prevention of mental disorders. Evidence is steadily growing for the relation between nutrition deficiencies, diet quality and mental health and for the efficacy and use of nutritional supplements to address deficiencies or as augmentation therapies. We advocate recognition of diet and nutrition as crucial factors in prevention and management of mental disorders.

Keywords: *Adolescents, depression, diet, mental health, nutritional neuroscience, systematic review*

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Introduction

Depression is defined as a cluster of specific symptoms with associated impairment affecting 7.4% of the adolescents (10–14 years) globally.[1] The clinical and diagnostic features of the disorder are broadly similar in adolescents and adults.[2,3] Research suggests that depression in adolescent is an early on-set sub form of the equivalent adult disorder; it has strong linkage with the recurrence later in life. The illness in adolescents and adults has similar clinical features and patterns of neural activity.[4] Due to the associated symptoms such as mood reactivity and irritability, depression in adolescents is more often missed than in adults. Also, due to primary presenting problems like anxiety, eating disorders, refusal to attend school, decline in academic performance, unexplained physical symptoms or behavioral problems, it remains unnoticed.[5] Furthermore data from findings of recent systematic reviews and meta-analysis concludes a significant evidence of association between unhealthy eating patterns and poor mental health among children and adolescents.[6] Also high intakes of fruit, vegetables, fish, and whole grains may be associated with a reduced depression risk in adults[7] and adherence to a Mediterranean diet may contribute to the prevention of a series of brain diseases.[8] Most mental disorders begin during youth but are detected for the first time in later life. Self-harm and suicide are the leading cause of death in young people. Poor mental health is associated with overall health and developmental concerns among youth; like educational achievements, reproductive and sexual health, substance abuse and violence. Even in wealthier societies, the needs of mental health care services are unmet, with worse situations in developing countries. Therefore, there is a need to understand the patterns of onset of psychiatric disorders during childhood and adolescence, transitioning into adulthood.[9] Thus it is also important to prevent, recognize and treat this disorder. The current systematic review represents an updated comprehensive data about

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depression in adolescents, its mechanism and the role of nutrition in prevention and treatment.

Methodology

Literature search

Relevant articles were identified by systematic online search from 6 electronic databases, i.e., PubMed, PsycInfo, Science Direct, MEDLINE, Scopus, and Google Scholar. The articles and research studies published between January 1978 and December 2017 were selected. Relevant keywords relating to depression, in combination with (and/or) mechanisms, psychosocial risk factors, nutritional medicine, food, nutrition, malnutrition, mental health, adolescents and/or clinical trials, interventions, randomized control trials, longitudinal studies, cross-sectional studies were used to extract articles. Additional publications were identified from references cited in the original articles.

Inclusion - Exclusion criteria

Studies considered for inclusion in this review
(1) Full-text articles;
(2) Published in English;
(3) Primarily conducted on humans
(4) Studies conducted on children, adolescents and adults;

We excluded studies that:
(1) Examined impact of medication on mental health;
(2) Used psychological therapies as a treatment for psychosocial problems;
(3) Were published in languages other than English

Data extraction

We screened potentially relevant articles for eligibility based on titles and abstracts. If they met the eligibility criteria, the full text publication was retrieved and reviewed. The reference lists of relevant articles were also screened to include additional studies. Full text articles were retrieved if the citation was considered eligible and was subjected to a second evaluation. Data were extracted from selected studies and details are presented below.

Results

Study selection

A flowchart detailing the study selection process is shown in Figure 1. The initial search yielded 1100 citations of which 965 were excluded upon initial screening for not meeting inclusion criteria. Of the remaining 135, 43 were excluded for the following reasons: not a target population, did not include a target outcome, not a relevant intervention, not a target study design, insufficient detail of dietary

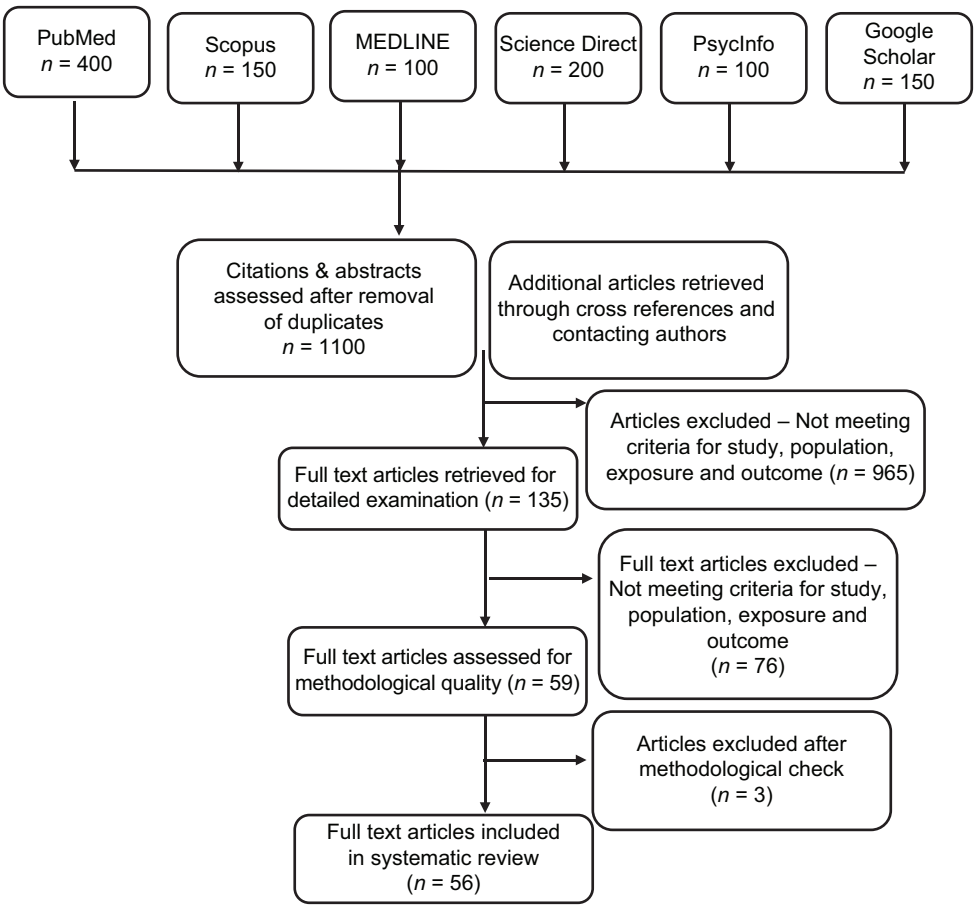

Figure 1: Flowchart of study selection process

intervention and not a validated measure of mental health outcomes. 50 studies fulfilled the inclusion criteria and additional 6 studies were screened through the reference list and citations. Overall, 56 studies were included in the review. The nutritional factors which play an important role in the etiology of depression are discussed below.

Nutrition risk factors in mental health disorders

"**Nutritional neuroscience**[10,11] is an emerging research field exploring the **nutritional factors** linked with human cognition, behavior and emotions."

A robust research evidence suggests that diet is to mental health, across the lifespan, although there are particular periods of rapid development. Prenatal and postnatal diet is important to the mental health of the mother[12] but also has implications for mental development and cognition of her offspring.[13,14] This suggests the potential to target the nutritional status of a woman during pregnancy in order to positively influence future mental health outcomes in children and adolescents.[15]

As in other domains of health, childhood experiences have an impact on the future health of the adolescent.[16] Unfortunately, many studies have reported that young people are eating well below dietary recommendations. They are increasingly reliant on nutrient poor, foods high in sugar and saturated fatty acids such as soft drinks, confectionary items, and baked snacks. These dietary patterns are not only significantly related to obesity and non-communicable diseases, but they also critically impact the brain development and mental health as well.[17] Consumption of diet and snack like foods has been linked to behavioral and emotional problems in children, which has been linked to mental disorders in adulthood.[18]

During adolescence, teenagers have greater independence to food choices and begin to establish dietary habits that will carry through adulthood.[19] This period is also critical, as it is typically during this phase that mental disorders emerge for the first time.[20] Globally, researchers have consistently demonstrated that diet quality is important to mental health of young people transitioning into adulthood.[20-22] Existing systematic reviews confirm a relationship between diet quality and mental health in children and adolescence.[23] This research evidence suggests the importance of establishing snack like foods with nutrient rich diets that support brain development and lays the foundation for a healthy adulthood.[6]

Depression is perceived as a biochemical based mental health disorder, while nutrition can impact its onset, severity and duration. Noticeable food patterns (like poor appetite, skipping meals, and a dominant desire for sweet foods) which precede depression are the same as those occurring during depression.

Research suggests that dietary patterns in Asian and American countries are often deficient in nutrients, especially vitamins, minerals, and omega-3 fatty acids. Also, a similar pattern of dietary intake is observed (diets deficient in vitamins, minerals, and omega-3 fatty acids) among patients with mental disorders. Studies have indicated that daily supplementation of these vital nutrients is often effective in reducing the symptoms of the patients. Amino acids supplements have also been found to reduce symptoms, as they are converted to neurotransmitters which in turn alleviate depression and other mental health disorders. On the basis of accumulating research evidence, diet therapy or modifications in the diet may be appropriate in controlling and preventing depression, anxiety, eating disorders, schizophrenia, and addictions.

Discussion

With special relevance to depression, various significant nutrients are discussed below.

Proteins

Proteins (amino acids) are the building blocks of life. Our body manufactures 12 amino acids and the remaining 8 have to be supplied by the diet (essential amino acids). High biological value protein foods like meats, eggs, milk and dairy products are rich in good quality protein and provide essential amino acids. Plant-based proteins such as peas, beans, and grains are low biological value protein and may lack one or two essential amino acids. Dietary intake of protein (intake of individual amino acids) can affect the brain functioning and mental health. Furthermore, many of the neurotransmitters in the brain are made from amino acids. For example, the amino acids tryptophan and tyrosine are precursors of neurotransmitters serotonin and dopamine. Low dietary intake of these amino acids results in reduced synthesis of the respective neurotransmitters, which is associated with low mood and aggression in patients.[24]

There are often two sides of depression feeling apathetic and unmotivated and feeling miserable. The most prevalent biochemical theory describing the cause of these feelings is a brain imbalance in two families of neurotransmitters.[25] There are:

- Serotonin, primarily influences mood
- Dopamine, noradrenaline and adrenaline, primarily influences motivation.

Figure 2 shows those nutrients that are essential for the production of serotonin, dopamine, adrenaline, and noradrenaline.

If a person is suffering from low mood, feels tense and irritable, is tired all the time, tends to comfort eat, has sleeping problems, the chances are they are short on serotonin. Table 1 summaries the effect of deficiency of the neurotransmitters, the foods that will make the deficiency worse and those that will improve the symptoms.

Serotonin is made from the amino acid tryptophan, a constituent of protein. Dr Philip Cowen and colleagues

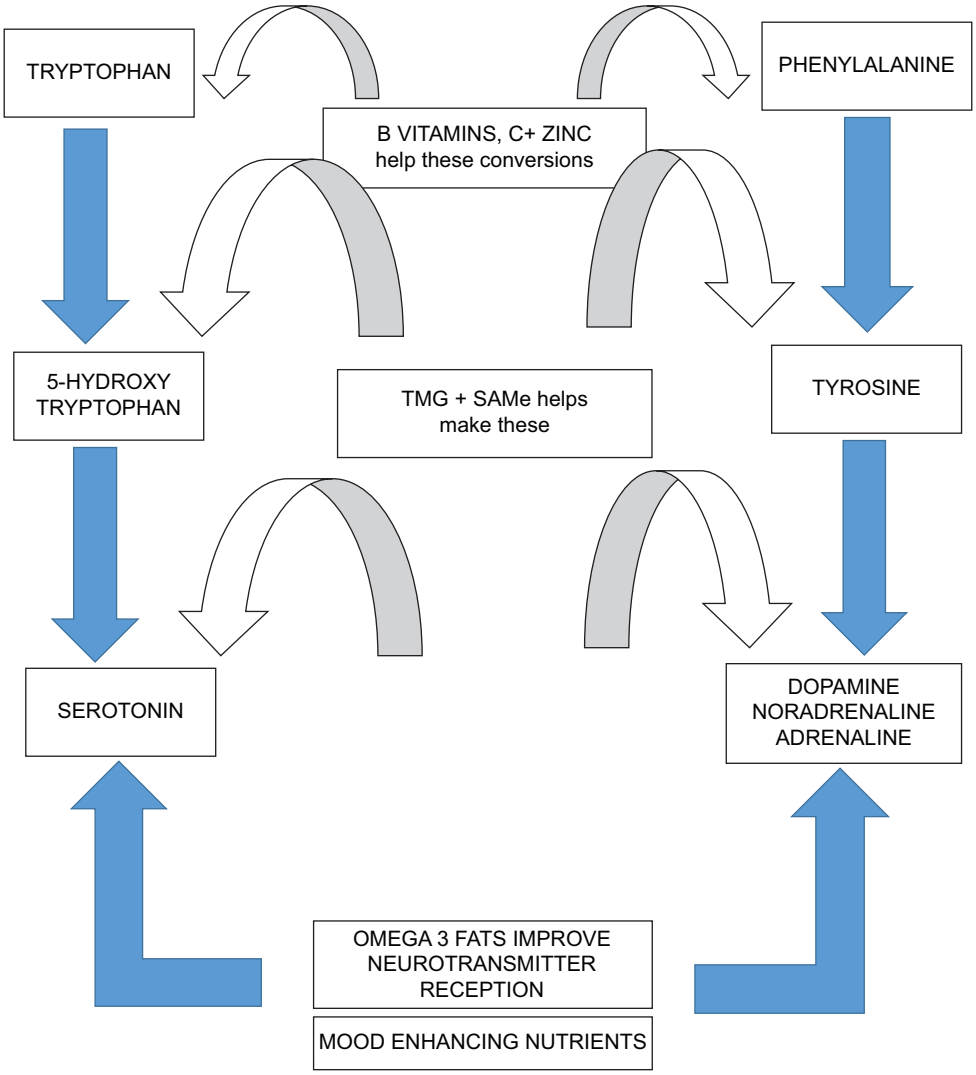

Figure 2: Nutrients that make mood enhancing neurotransmitters. Source: Adapted from Holford, 2003; Depression: the nutrition connection. Primary Care Mental Health 1: 9-16

from the University of Oxford, UK, conducted a trail on 15 volunteers who had history of depression, but were currently not depressed. They gave these volunteers a nutritionally balanced drink, that excluded tryptophan. Within seven hours from the consumption of the drink, 10 out of 15 participants noticed a worsening of their mood and started to show signs of depression. On being given the same drink, but this time with added tryptophan, their mood improved. The recommended dosage of this amino acid is 100 mg of 5 Hydroxy Tryptophan (5-HTP), two or three times a day, for depression. Some supplements also provide vitamins and minerals such as B12 and folic acid, which may be even more effective because these nutrients help to turn 5-HTP into serotonin.[26]

Another group of neurotransmitters associated with lack of motivation and depression are catecholamines—dopamine, noradrenaline and adrenaline. As discussed in Figure 2, both adrenaline and noradrenaline are synthesized from dopamine, which is made from the amino acid phenylalanine.

A group of researchers from Chicago, screened depressed patients by testing phenylethylamine in the blood; low levels meant, more amounts of phenylethylamine. They supplemented 40 depressed patients with supplements of phenylalanine and 31 of them showed improved symptoms.[27]

Tyrosine also has been shown to work well in those with dopamine-dependent depression. A pilot study conducted on 12 patients in France concluded that administration of 3200 mg of tyrosine a day showed significant improvement in mood and sleep on the very first day.[28]

Research suggests that best results are achieved by supplementing all these amino acids - 5-HTP, phenylalanine and tyrosine - together with the B group vitamins (B6, B12) and folic acid which help turn them into neurotransmitters.

Table 1: Deficiency of neurotransmitter and their relationship with food

Neurotransmitter	Effects of deficiency	Foods to avoid	Foods to consume
Acetylcholine	Deterioration of memory and imagination	Sugar	Organic/free-range eggs
	Fewer dreams	Deep-fried foods	Organic or wild fish - especially salmon, mackerel, sardines and fresh tuna
	Increased confusion, forgetfulness and disorganisation	Junk foods	
		Refined and processed foods	
		Cigarettes	
		Alcohol	
Serotonin	Low mood	Alcohol	Fish
	Difficulty sleeping		Fruits
	Feeling "disconnected"		Eggs
	Lacking joy		Avocado
			Wheatgerm
			Low-fat cheese
			Lean, organic poultry
Dopamine	Lacking drive, motivation and/or enthusiasm	Tea and coffee	Regular, balanced meals
	Crave stimulants	Caffeinated drinks and pills	Fruits and vegetables high in vitamin C
			Wheatgerm
			Fermented products
Gamma-Amino Butyric Acid (GABA)	Hard to relax	Sugar	Dark green vegetables
	Anxious about things	Alcohol	Seeds and nuts
	Irritable	Tea and Coffee	Potatoes
	Self-critical	Caffeinated drinks	Bananas
			Eggs

Source: Adapted from[26] Holford, 2003; Depression: the nutrition connection. Primary Care Mental Health 1:9-16

SAMe and TMG: The natural antidepressants

SAMe and TMG stand for s-adenosyl methionine and tri-methyl-glycine, respectively. These two strange sounding nutrients are kind of amino acids. They are methyl group donors and can lower homocysteine levels by donating methyl groups.

SAMe is the most comprehensively studied natural antidepressants. Many placebo-controlled, double-blind studies have shown that SAMe is equal to or superior to antidepressants, works faster (within few days, whereas pharmaceutical antidepressants may take 3–6 weeks to show effect). The recommended allowance is 200–600 mg a day, but it is very expensive and unstable. An alternative which is less costly and more stable is TMG. In the body it turns into SAMe, but the quantity is three times i.e., 600–2000 mg a day, on an empty stomach or with a fruit.[29-31]

Omega 3 fatty acids

Brain has the highest levels of lipids. These brain lipids (composed of fatty acids) are structural constituents of membranes. Gray matter in the brain contains 50% polyunsaturated fatty acids (33% are omega-3) and are supplied through diet. N-3 PUFAs modulate the mechanism of brain neuron communication. Decosahexanoic Acid (DHA) predominantly constitutes 15% of the brain, whereas EPA constitutes 0.2%. Therefore, DHA concentration affects the membrane permeability of cells in Central Nervous System (CNS) and deficiency of DHA is linked with the dysfunction and impaired transmission neurotransmitters; serotonin, norepinephrine, and dopamine. Phospholipids of neural cell membrane are composed of PUFAs. N-3 PUFAs and fish consumption have been connected to the inflammation theory.[32]

Omega - 3 fats have a direct influence on serotonin status by enhancing its production and reception. According to Dr JR Hibbeln,[33] who discovered that fish eaters are less prone to depression, described the process as "It's like building more serotonin factories, instead of just increasing the efficiency of serotonin you have."

Research suggests that depletion of n-3 PUFAs can be an etiological factor in several neuropsychiatric disorders including depression. Lower intake or concentrations of n-3 PUFAs is observed in depressed individuals.[34] Fish intake of >150 g/week is linked to decreased levels of proinflammatory markers like C Reactive Protein (CRP) and cytokines such as interleukin-6. This supports the hypothesis that eating more fish could lead to reduced depressive symptoms through modification of inflammatory process.[35]

Another researcher from London's Hammersmith Hospital, UK reported a case study of a 21-year-old student who had been on a variety of antidepressants, but had shown no improvement. He had a very low sense of esteem, little appetite, sleeping problems, found it hard to socialize and often thought of killing himself. After 1 month of supplementation with ethyle-EPA (eicosapentaenoic acid), a concentrated form of omega-3, he was no longer having suicidal thoughts and after 9 months of supplementation, no longer had depression.[36]

Evidence [Table 2] also suggests that, there are a number of associated mechanisms observed in neural systems of individuals with depression and those affected in dietary deficiency of omega 3 PUFAs;

- Altered levels of neurotransmitters
- Reduce glucose metabolism in brain
- Decreased levels of brain derived neurotrophic factor.

Supplementation trails with omega 3 PUFAs have shown positive effects in depression. In a double blind trial, 20 subjects with major depressive disorders received (randomly) 3.3 g/day of EPA + DHA (fish oil) or placebo for 8 weeks in addition to the usual treatment. Patients who received PUFA (EPA + DHA) supplementation had lower scores on the depression scale.[37]

Noaghuil and Hibbeln[38] investigated cross-national prevalence rates of bipolar disorders and concluded that there is a strong relationship between increased sea food consumption and lower prevalence rates. Regular consumption of fish has also been associated with reduced suicidal ideation and better self-reported status of mental health.

B Group Vitamins

B group vitamins act as co-factors in key enzymes that control the production and balance of neurotransmitters. For example, serotonin (5-HT) is produced from 5-HTP by addition of a methyl group (carboxylase) as is adrenaline from noradrenaline. This process is highly dependent on vitamin B12, B6, and folate. Folate deficiency is extremely common among depressed patients.[39] A study conducted at Depression and Clinical Research Program at Boston Massachusetts General Hospital, USA on 213 depressed patients, reported that people with lower folate levels had more "melancholic" depression.[40]

Another research on people diagnosed with depression and schizophrenia was conducted at Kings College Hospital, London, UK.[41] The researchers found that one in three of these patients had borderline or definite folate deficiency. These patients than took part in a supplementation trial, where they took folate for 6 months. Post 6 months supplementation trail, these patients had significantly improved recovery and the longer they took folate, better they felt.

Folate

After conception of the fetus, intake of folate is important for the formation of the neural tube, development of brain and nervous system, normal growth, nucleotide synthesis as well as programmed cell death. Research suggests that deficiency of folate may affect one-third of psychiatric patients. This could be due to disturbed appetite, lowered intake, altered absorption or increased requirement.[42] Interestingly, individuals with megaloblastic anemia have been reported to have neuropsychiatric problems, and depression is the most common neuropsychiatric manifestation of folate deficiency.[43] However, folate deficiency and depression are interconnected, it is not clear whether depression leads to folate deficiency or primary folate deficiency is a cause of depression. Deficiency of folate can lead to irregularities in methylation and synthesis of monoamine neurotransmitters. Different forms of folate share an inter conversion potential and are present in the pathways of carbon cycles impacting the synthesis of dopamine, serotonin and norepinephrine.[44]

Folate in the form of methylenetetrahydrofolate (MTHF) is required in the methylation process of homocysteine

Table 2: Comparison of effects of depression and omega 3 PUFA on neural parameters

Mechanism	Depression	Deficiency of omega 3 PUFA	Addition of omega 3 PUFA
Neurotransmission	Treatment maintains levels of neurotransmitters	Decreased levels of dopamine and D2 receptor	Increased levels of dopamine and increased binding to D2 receptor
Glucose metabolism in brain	Reduced metabolism.	Increased by treatment with lithium.	Reduced uptake of glucose via glucose transporter
AA metabolism in brain	Treatment reduces AA turnover and metabolism	Increases AA turnover and metabolism	
Pro-inflammatory cytokine levels	Increased		Reduced
Neuronal atrophy	Increased		DHA promotes neural cell growth and reduces apoptosis
BDNF levels in brain	Decreased (restored by antidepressant treatment)	Decreased by deficiency, diets high in saturated fat and sucrose and COX inhibitor	Increased by omega 3 PUFA, exercise, vitamin E, and prostaglandins

Source: Adapted from[40] Sinclair *et al*., 2007. Omega 3 fatty acids and the brain: Review of studies in depression

(a sulphureted amino acid) back to methionine. Homocysteine present in meat, fish, cheese, egg and poultry is derived from dietary methionine. Elevated levels of blood homocysteine is a functional marker of folate deficiency and is linked to the prevalence of depression. In addition to this, homocysteine is suggested to have neurotoxic effects.[45] Several other methylation reactions, like the synthesis of S-adenosyl-methionine (SAMe, the vital methyl donor) require MTHF. Anti-depressant properties of SAMe have also been suggested.[46]

Vitamin B12

Cognitive changes are observed in adolescents with borderline levels of vitamin B12 deficiency. In elderly, supplementation with cobalamin enhances cerebral and cognitive functions, delays onset of dementia and enhances language function of people with cognitive disorders.[47]

Minerals

Zinc

Zinc is an important mineral involved in the process of gustation (taste perception). It also protects the brain cells against the potential damage caused by free radicals. In patients with clinical depression, zinc levels are lowered. Intervention research suggest that oral zinc supplementation can influence the effectiveness of antidepressants, such as imipramine.[48]

A placebo-controlled, double blind trial of zinc supplementation in antidepressant therapy was conducted in patients who had major (unipolar) depression. Patients received zinc supplementation (6 patients; 25 mg of Zn2+ once daily) or placebo (8 patients) and were treated with standard antidepressant therapy (tricyclic antidepressants, selective serotonin reuptake inhibitors). Zinc supplementation significantly reduced scores in both measures after 6- and 12-week supplementation when compared with placebo treatment. This supplementation trail is the first demonstration of the benefit of zinc supplementation in antidepressant therapy.[49]

Iron

Iron is necessary for the synthesis of neurotransmitters and myelin, production of energy in the cerebral parenchyma and oxygenation. Iron deficiency anemia is associated depression, apathy and fatigue, affecting adolescent girls and women in the child bearing age. Fatigue, lethargy, and depression can all be symptoms of iron deficiency, which has led to studies investigating the relationship between circulating levels of iron and depression.[50,51] Iron concentrations in the umbilical artery are important for the fetal development and IQ in children.[52]

Major Depressive Disorder (MDD) in adolescents is often persisting or reappearing in adult life. MDD has also been associated with inflammation and changes in iron measures, such as decreased serum transferrin levels.[53] However, these studies are few in number, particularly for adolescents.

Iodine

The role of iodine in the brain development is well established. Iodine provided by the thyroid hormone regulates the energy metabolism of the cerebral cells. During pregnancy, deficiency of iodine results in Iodine Deficiency Disorders (IDD) which induces cerebral dysfunction, eventually leading to mental retardation and cretinism.[54]

Conclusions

Micronutrient deficiencies and malnutrition can impact the physical and mental development of a child. Given that the average age of onset for anxiety and mood disorders is 6 years and 13 years, respectively[50] the potential for early intervention using strategies targeted at improving dietary intake at a population level may be of substantial public health benefit.

Though, depression is considered as a cause of global disability among adolescents, many knowledge and research gaps still exist. Due to the immense burden of mental disorders, preventive treatment strategies and modifiable risk factors need to be identified. Furthermore, in low and middle income countries, development of cost-effective methods for detection, assessment and treatment of depression is required. In-depth research is required in reporting and understanding prevalence, causes and mechanisms underlying depression throughout lifespan.

Diet and nutrition offer key modifiable targets for the prevention of mental disorders, having a fundamental role in the promotion of mental health. The area of nutritional neuroscience needs to be promoted for the prevention and management of depression (and other mental disorders) through a healthy diet. Further research is required in this regard because significant evidence linking diet (quality, eating pattern, and specific nutrients) and mental health among children and adolescents is now available.[6,7,45,52-54] Research is further required to establish the use, efficacy and dosage of nutrients (composition and constituents of a diet) in individuals with and without mental disorders. This further needs to framed into public health policies and programs. Nutritional medicine should now be considered as a mainstream element of psychiatric practice, with research, education, policy, and health promotion supporting this new framework.[45]

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Conflicts of interest

There are no conflicts of interest.

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