# Chapter 8
# Nutrition and Depression

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**Abstract** Nutrition plays a variety of physiological roles in the maintenance of mental health, with some potential pathological participations as well. Indeed, suboptimal and anormal nutrition may be implicated in the underlying pathology of mental health disorders and may interfere with treatment response and recovery. Nutrient deficiency is widespread throughout the world, affecting in particular, but not only, low- and middle-income countries and individuals disproportionately. Therefore, the socially and economically disadvantaged population is at a higher risk of major mental health disorders, including depression. Robust recent data relates the poor nutrition or nutritional deficiency (e.g., dietary antioxidants, trace elements) to major depressive disorders. On the contrary, nutrients (e.g., essential fatty acids and folic acid) may be used effectively to treat depression or to augment the existing treatments. The purpose of this chapter is to discuss the current evidence regarding the role of nutrition in depression.

**Keywords** Behavioral health disorders · Diet · Depression · Gut-brain axis · Major depressive disorder · Nutrition · Serotonin · Treatment management · Tryptophan · Vitamin

## 8.1 Introduction

Depressive disorders are common and have been identified as the leading cause of global disease burden. They mainly include major depressive disorder (MDD), dysthymia, and bipolar disorder. The symptoms of MDD comprise disturbed sleep or appetite, loss of interest or pleasure, low mood, feelings of guilt or low self-worth, fatigue, poor concentration, and suicidal thoughts. In addition, patients affected by MDD are at increased risk of suicide.

The neuroendocrine, immunological, metabolic, and neurotransmitter systems (e.g., serotonin, gamma-aminobutyric acid) are impaired in patients with MDD. Gender, socioeconomic level, social support, stress, alcohol and drug use, genetic and epigenetic variables, inflammation, physical conditions, and food are the main risk factors that increase the chance of developing depressive disorders. Recently, there has been a growing body of evidence pointing to a link between food and depression, and nutritional deficiencies are linked to the underlying pathophysiology of depression. The neurotransmitters like serotonin, dopamine, and norepinephrine regulate mood, appetite, and cognition (Sarris et al. 2015). The tryptophan, vitamin B6, vitamin B12, folic acid, phenylalanine, tyrosine, histidine, choline, and glutamic acid are required for the synthesis of these neurotransmitters.

Furthermore, some nutrients, such as marine-derived omega-3 fatty acids, influence serotonergic and dopaminergic neurotransmission and can help to alleviate depressive symptoms (Lin et al. 2010). As a result, poor diet quality and insufficient nutritional consumption represent risk factors for depression of new rising interest for clinical as well as for scientific research. Indeed, healthy eating habits can lower

the incidence of depression, according to a meta-analysis of 21 observational studies (Li et al. 2017). Further, nutritional status contributes to the proper function of the innate immune system and hypothalamic–pituitary–adrenal (HPA) axis. The importance that the diet plays in the pathophysiology of depression also lies in the possibility of intervening in a clear and rapid manner on it. In this regard, diet, physical activity, and social interaction are modifiable lifestyle factors that have been shown to reduce the prevalence of depression (Worrall et al. 2020). Accordingly, correction of nutrient deficiencies may help in the prevention and management of depression. In this chapter, we discuss the role of nutrition or diet under the following headings: epidemiology, dietary patterns, foods/food groups, and nutrients.

## 8.2 Epidemiology

According to recent data, depression affects up to 13.3% of youths aged 12–17 years and 7.1% of adults aged older than 18 years, thus explaining why it is considered a high global public health priority (Substance Abuse and Mental Health Services Administration 2018). Indeed, its elevated high prevalence and the resulting severe disease burden with economic, personal, and healthcare consequences contribute to make MDD the second greatest contributor to global disease burden quantified as years of life lived in less-than-ideal health (Vos et al. 2012). The exact causes of depression are still far from being fully understood, but today we consider an interaction between genetic and epigenetic factors, gender, childhood adversities, socioeconomic status, job availability, social support, concomitant treatments, stress, alcohol and drug use, inflammation, microbiome, medical comorbidities, endothelial dysfunction, and diet (Bodnar and Wisner 2005; Kris-Etherton et al. 2021; Payne 2010). However, the epidemiology, as well as the causative link, becomes even more vague and evasive when considering the relationship between depression and nutrition.

### *8.2.1 Dietary Patterns*

#### 8.2.1.1 Dietary Inflammatory Index (DII)

The etiological model of depression explains the strong association between inflammation and depression (C.-H. Lee and Giuliani 2019; Zunszain et al. 2013). Dietary inflammatory index (DII) is a measure that indicates the pro-inflammatory potential of certain diets. It is known that certain diets increase the level of inflammatory cytokines in blood (Kanauchi et al. 2019; Liu et al. 2021; Saghafi-Asl et al. 2021; Shivappa et al. 2014). Higher adherence to the Mediterranean diet and a lower DII have been associated with a lower risk of depressive outcomes (Lassale et al. 2019).

Hence, diets with high DII are more likely leading to depression. Interestingly, the increase in depressive disorders over the past few decades parallels a decline in healthy lifestyle behaviors, including poorer diet quality (Benjamin et al. 2019). Depression is known to affect appetite; therefore, cross-sectional evidence of an association between diet and depression may reflect reverse causation.

Higher intake of both vegetables and fruits was associated with a lower risk of depression, whereas higher inflammatory diets and a dietary pattern rich in Western foods were associated with an increased risk of depression. A 2020 meta-analysis of 18 studies examining the relationship between diet and depression in elderly population reported that a healthy dietary pattern was associated with a reduced risk of depression (Wu et al. 2021). The relationship between nutrition and depression changes with age (Chang et al. 2016; Vermeulen et al. 2016). Further, a meta-analysis found no link between a Mediterranean diet, a "healthy" diet, or fish consumption and depression in old adults (Matison et al. 2021).

## *8.2.2 Epidemiological Evidence Relating Dietary Patterns to Depression*

### 8.2.2.1 Mediterranean Diet

Mediterranean diet was firstly defined as that by Ancel Keys as observed in Southern Italy and Greece during the 1960s (Davis et al. 2015). This term is used to refer to a dietary pattern that uses olive oil as a major source of monounsaturated fats and is typically high on fresh fruits, vegetables, legumes, nuts, and whole grains. Fish, dairy, and poultry in small-to-moderate amounts are tolerated, but red meat consumption is discouraged.

According to Seven Countries Study, Mediterranean diet is associated with reduced risk of coronary heart disease (CHD) and cardiovascular diseases (CVD) compared to northern European countries and the United States after 25-year follow-up (Kromhout et al. 1995; Menotti et al. 1999). Moreover, there is data also supporting the idea that a Mediterranean-style dietary pattern lowers the risk of depression. A Mediterranean-style dietary intervention that included cooking classes, food hampers, and fish oil supplementation (900 mg/day docosahexaenoic acid [DHA] and 200 mg/day eicosapentaenoic acids [EPA]) improved adherence to the Mediterranean diet, reduced depression, and improved mental health-related quality of life (Parletta et al. 2019).

However, according to a recent meta-analysis, there was no difference in incident depression between participants in the highest and lowest categories of Mediterranean diet adherence (Li et al. 2017; Rienks et al. 2013). These differences may be attributed to methodological or clinical heterogeneity between studies. In addition, it should be taken into account that Mediterranean diet is more common in countries more exposed to the sun, with a mild climate and with more hours of light in the day, conditions that have always been associated with an improvement in depression,

thus acting as a confounding factor (Abraham et al. 2021; Murphy and Parletta 2018). Therefore, the debate is still open.

#### 8.2.2.2 Dietary Inflammatory Index/Alternative Dietary Inflammatory Index

Either the original DII (Sánchez-Villegas et al. 2015; Shivappa et al. 2014) or the alternate DII (Adjibade et al. 2019) is used to assess the relationship between the level of inflammation in the diet and the risk of depression. The highest category of inflammatory diet is associated with a higher risk of depression. Also, the switch from the lowest to the highest category of inflammatory diet is associated with increase in depression incidence (Matison et al. 2021). Lucas et al. (2014) identified that the highest category of inflammatory diet is associated with increased levels of biomarkers of inflammation (Lucas et al. 2014). Overall, there is a detrimental association between the DII and incident depression.

#### 8.2.2.3 "Healthy" Diet

Adherence to dietary guidelines is defined as a healthy dietary pattern (Das et al. 2021; Lai et al. 2017; Voortman et al. 2017). However, some studies used an a posteriori method to identify dietary patterns, which they labeled "prudent" (Chocano-Bedoya et al. 2013; Jacka et al. 2014), "whole food"(Akbaraly et al. 2009), or "vegetables-fruits" (Chan et al. 2014). Results showed that healthy dietary patterns are associated with less depressive symptoms. Lower odds of depression were linked to greater adherence to healthy/prudent, Mediterranean, pro-vegetarian (i.e., higher in plant foods than animal foods), and Tuscan dietary patterns. Increased nutrition quality was also linked to a lower incidence of depression (Molendijk et al. 2018). High intakes of fruits, vegetables, seafood, and whole grains characterized these healthy dietary patterns. Dietary patterns that included fish, olive oil, vegetables, fruits, and nuts were linked to a lower risk of depression (Martínez-González and Sánchez-Villegas 2016). In particular, the Tuscan diet takes its name from the homonymous northern Italian region famous for its healthy and local cuisine. In details, it is characterized by fish, olive oil, several vegetables, fruits, potatoes, cereals, eggs, wine, red and processed meat, and other sauces (particularly tomato sauce). This dietary pattern reflects a typical Tuscan diet and was therefore labeled as "typical Tuscan dietary pattern (Vermeulen et al. 2016)."

#### 8.2.2.4 High-Fat/Sugar Diet

This dietary pattern is labeled as "convenience" (Gougeon et al. 2015), "Western" (Rienks et al. 2013), or "processed food" (Akbaraly et al. 2009). Overall, participants in the highest category of consumption of this diet or ultra-processed food had a

higher risk of depression. Further, the switch from the lowest to the highest category is associated with increase in the incidence of depression (Matison et al. 2021). Indeed, this diet category, which mainly includes fast and "junk food," presents an important impact on immunological system with many implications on mental and physical health, also through the Western diet-microbiome-host interaction (Myles 2014).

#### 8.2.2.5 Other Dietary Patterns

There are a multitude of diets and dietary patterns that can be examined to study their association with physical and mental disorders, and depression in particular. Among them, we highlight the consumption of a traditional Taiwanese diet, which reported a higher incidence of depression among older adults, whereas higher consumption of a traditional Canadian diet was not associated with incident depression among those aged 67–84 years (Gougeon et al. 2015). Consumption of carbohydrates with a higher glycemic index was associated with higher depressive outcomes (Gangwisch et al. 2015). On the other hand, higher consumption of a "varied," "snacks-drinks-milk," "dairy," "meat-fish," "meat-processed/meat," "cooked vegetable," and "fruit" dietary pattern was not associated with longitudinal risk of incident depression (Matison et al. 2021). Other healthy dietary patterns, such as the Dietary Approaches to Stop Hypertension (DASH) diet (high in fruits, vegetables, and low-fat dairy, and low in saturated fat), have improved depressive symptoms. Overall, these studies imply that eating a nutritious diet that includes vegetables and fruits, fish, olive oil, nuts, and grains, in accordance with current dietary recommendations, may help to alleviate depressed symptoms. The risk of depression has been linked to vegetarian dietary patterns in a mixed bag of ways. Similarly, some studies have found a correlation between decreased meat consumption and an increased risk of depression, while others have found no such link.

#### 8.2.2.6 Specific Food Components

Vegetables, fruits, and fish servings can be classified, and they are linked with depression (Matison et al. 2021) (Table 8.1).

#### 8.2.2.7 Red Meat and Processed Meat

A pooled estimate of the association between red and processed meat consumption and depression observed a small but significant increase in the risk of depression in a meta-analysis. However, the analysis was limited by high heterogeneity (Nucci et al. 2020).

**Table 8.1** Specific food components and risk of depression

| Food servings | Categories | Risk of depression |
|---|---|---|
| Vegetable servings | • Five categories (0–1/day, 2/day, 3/day, 4/day, and ≥5/day) (Shang et al. 2020)<br>• Three categories (0–1/day, 2–4/day, and ≥5/day) (Mihrshahi et al. 2015)<br>• Two categories (≤5/week and ≥6/week) (Chi et al. 2016) | • The shifting from the lowest to the highest category of vegetable intake is associated with a lower risk of depression (Matison et al. 2021) |
| Fruit servings | • Two categories (≤5/week and ≥6/week) (Chi et al. 2016) or <2/day and ≥2/day (Mihrshahi et al. 2015)<br>• Four categories (none, 1/day, 2/day, and ≥3/day) (Shang et al. 2020) | • Highest intake of fruit is associated with lower risk of depression<br>• The shifting from the lowest to the highest category of fruit intake is associated with a lower risk of depression<br>• Further, the higher consumption of citrus fruit and juices is associated with lower risk of depression |
| Fish | • Two categories (≥3/week and <3/week) (Almeida et al. 2013; Tsai et al. 2012)<br>• Five categories (<1/month, 1–3/month, 1/week, 2–4/week and ≥5/week) (Lucas et al. 2011) | • There was no association between fish intake and incident depression<br>• Furthermore, in a Taiwanese study of older adults, higher seafood consumption was not associated with an increased risk of depression (Tsai et al. 2012) |

#### 8.2.2.8 Other Food Types

Tea

The difficulty in studying the association between tea and depression also lies in the different types of existing tea, and the different methods of preparation and frequency of consumption, which can influence its effectiveness (Mancini et al. 2017). A Taiwanese study reported that higher tea consumption (mainly oolong tea) is associated with reduced incidence of depression (Chi et al. 2016), whereas the studies conducted in the United States found that hot or iced tea is not associated with depression (Chang et al. 2016; Guo et al. 2014); however, a detrimental association was noted with intake of decaffeinated iced tea (Guo et al. 2014).

Coffee and Caffeine

Similarly to what is considered for tea, the methods of cultivation and consumption of coffee are also varied and diversified all over the world (Ding et al. 2014). A higher caffeinated coffee intake was found to be related with lower incidence of depression (Guo et al. 2014; Lucas 2011); however, no such association was noted

with decaffeinated coffee. Combined intake of caffeinated coffee and tea was not associated with the risk of depression (Ritchie et al. 2014).

Analysis of the dose–response for caffeine intake and risk depression showed that caffeine was associated with nonsignificant decreased risk of depression only up to 300 mg/day (about 3–4 cups/day of coffee) (Grosso et al. 2016).

Grain

Higher whole-grain intake was associated with lower incidence of depression (Gangwisch et al. 2015). However, the non-whole grain-to-whole grain ratio was not associated with the risk of depression (Gangwisch et al. 2015).

Others

Increased risk of depression has been reported with higher intake of added sugar, but not total sugar (Gangwisch et al. 2015). Similarly, increased consumption of regular soft drinks, as well as increased consumption of diet soft drinks/fruit drinks/sweetened iced tea, is associated with an increased risk of depression (Guo et al. 2014). Results were mixed for studies that investigated associations with meat intake. Higher chicken consumption was associated with increased risk for depression (Shang et al. 2020), whereas meat (all types) (Almeida et al. 2013) as well as combined meat and poultry (Tsai et al. 2012) were not associated with depressive risk. Intake of dairy (Almeida et al. 2013; Tsai et al. 2012), legumes (Tsai et al. 2012), eggs (Tsai et al. 2012), nuts and seeds (Gangwisch et al. 2015), onions (Chang et al. 2016), cereal (Tsai et al. 2012), and alcohol (Tsai et al. 2012) was not associated with the risk of depression.

#### 8.2.2.9 Nutrients

Dietary nutrients are classified into two types: macronutrients and micronutrients (Fig. 8.1). Micronutrients are further classified into four types: vitamins, macrominerals, trace minerals, and organic acids.

#### 8.2.2.10 Macronutrients (Fig. 8.1)

A change in one macronutrient's intake causes a proportional shift in another macronutrient's intake. Hence, changing one macronutrient's intake cannot be done in isolation(s). Studies have reported that macronutrient consumption (total) is associated with depression and depressive symptoms. Furthermore, diets with varying macronutrient compositions have no effect on depressive symptoms, but weight-loss diets generally improve depressive symptoms (regardless of the

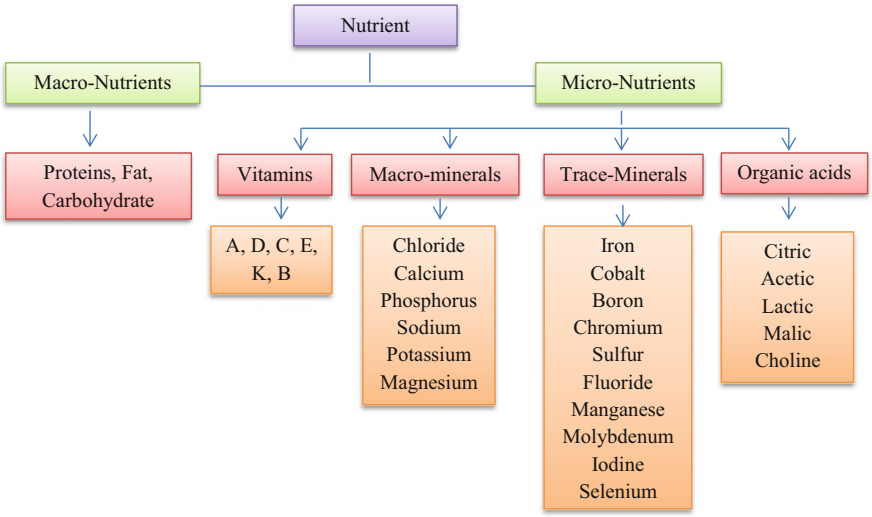


**Fig. 8.1** Classifications of dietary nutrients

macronutrient composition) (El Ghoch et al. 2016). The epidemiologic studies show a consistent relation among depression and dietary sources of macronutrients.

## Proteins

The National Health and Nutrition Examination Follow-Up Study showed that higher protein intake at baseline was associated with lower risk of severe depression. In contrast, among women, protein intake was not associated with depressed mood, but a higher percentage of energy from protein was associated with severity of depression. In a cross-sectional study of male Japanese workers at a manufacturing company, no association was observed between intake of protein, fat, and carbohydrate and depressive symptoms; however, plant protein intake was associated with lower odds of depression. In an Italian study, higher intake of fish/shellfish was associated with a decrease in depressive symptom. Notably, depressive symptoms were associated with a reduction in red or processed meat and an increase in dairy intake. However, this could be due to the reverse causality.

## Fat

Literature on fatty acids and their role in mood disorders has been growing in recent years. Several studies have shown positive benefits for omega-3 polyunsaturated fatty acid supplementation on symptoms of depression. These benefits were noted for eicosapentaenoic (EPA)-pure or EPA-major formulations but not

docosahexaenoic (DHA) acid-pure or DHA-major preparations. For optimum benefits, an EPA-major preparation at dosages $\leq$1gm/day is suggested for unipolar depression. It is important to note that the physiological effect of fatty acids differs by type (Sacks et al. 2017).

### Polyunsaturated Fatty Acid (PUFA)

Human body cannot synthesize the two families of essential long-chain PUFA: n-3 and n-6 fatty acids (Koletzko et al. 2008). Therefore, diets must contain either the n-3 or the n-6 PUFA or their precursor molecules (Table 8.2). Each parent fatty acid can be desaturated and elongated to a series of longer chain PUFAs. It is important to note that the synthesis of n-3 PUFA from α-linolenic acid in humans is inefficient, so humans are more dependent on seafood to meet their n-3 PUFA requirements.

Higher intake of the omega-6 PUFA, linoleic acid, was associated with increased risk of depression (Lucas et al. 2011). Furthermore, serum and dietary n-3 PUFA levels are low in patients with depression. Countries with lower levels of n-3 PUFA intake have higher rates of depression (Liperoti et al. 2009; Sontrop and Campbell 2006).

The n-3 PUFAs eicosapentaenoic acid and docosahexaenoic acid are the most biologically important for mental health and are most abundant in the brain. PUFAs are essential structural components of phospholipid membranes in all bodily tissues. They are particularly abundant in the brain, where they regulate the biophysical properties of neuronal membranes. Receptor activity, neurotransmitter absorption, and signal transmission are all affected by fatty acids. DHA is the most abundant n-3 PUFA in the brain. High DHA concentrations improve serotonin receptor sensitivity by increasing membrane fluidity. The n-3 PUFAs are also precursors to specific prostaglandins and leukotrienes, which are potent vasodilators and inhibitors of platelet aggregation. They reduce the inflammation.

In the United States, the ratio of n-6 PUFAs to n-3 PUFAs has been remarkably altered from about 1:1 before 1890 to between 10:1 and 25:1 in recent years. This shift in intake patterns, caused by a two- to threefold increase in intakes of vegetable oils at the expense of n-3 PUFAs from fish and plants, is thought to be responsible for the increased incidence of depressive disorders in the United States in the past century. Further, the concentrations of n-3 PUFAs in the blood have repeatedly been

**Table 8.2** PUFA and dietary source

| PUFA and its precursor | Dietary source |
|---|---|
| n-3 PUFA | Fatty fish and certain algae |
| Precursor of n-3 PUFA (-α-linolenic acid) | Flaxseed and walnuts |
| n-6 PUFA | In animals fed a high-cultivated cereal diet |
| Precursor of n-6 PUFA (linoleic acid) | Vegetable oil sources (e.g., maize, cottonseed, soya, and sunflower seed) |

shown to be lower and the ratio of n-6 to n-3 PUFAs has been shown to be higher in depressed individuals compared with healthy control subjects, with blood concentrations strongly correlated with the severity of the disorder.

The higher intake of fish, EPA plus DHA, and total n-3 PUFA is associated with lower risk of depression. Higher intake of added sugars and refined carbohydrates is positively associated with depression; in contrast, higher consumption of fiber, fish, and n-3 fats may be protective.

Carbohydrate

Total carbohydrate consumption is not associated with depression. More specifically, the higher intake of lactose and fiber is linked to a lower risk of depression, whereas no links were found between glucose, sucrose, fructose, or starch consumption and incident depression (Gangwisch et al. 2015). Also, in context with hypocaloric diet, macronutrient composition has limited deleterious effects on depressive symptoms in nondepressed individuals.

Compared to low-glycemic diet, a high-glycemic-load diet causes major mood alterations, increased fatigue, and depression symptoms. Prospective cohort studies have found that a higher intake of added sugars from sugar-sweetened beverages, refined carbohydrates, and sweet foods is associated with a higher risk of depression. Data from the Women's Health Initiative cohort showed that a higher intake of added sugars, but not total sugars or total carbohydrate intake, was associated with higher odds of incident depression. Further, higher intake of fiber was associated with a lower risk of incident depression in this cohort.

The quality of carbohydrates is more strongly related to depression risk than total carbohydrates.

The published studies have measured carbohydrate in diet using the Carbohydrate Quality Index (a measure of intake of higher quality carbohydrates) and the glycemic index. However, the glycemic index is not a reliable proxy for the glycemic response to carbohydrate intake.

According to current dietary recommendations, whole-grain carbohydrate sources should be preferred over refined carbohydrate sources. In some published studies, exercise has been linked to a reduction in depressive symptoms, and thus exercise may have blunted any potential diet-induced effects.

#### 8.2.2.11 Micronutrients

Micronutrients are essential for the optimal functioning of the central and peripheral nervous system. Inadequate intake of various micronutrients is linked to an increased risk of depression. Micronutrient-associated depressive disorders include vitamins (e.g., vitamin B6, vitamin B12, folic acid, and vitamin D) and minerals (e.g., zinc and magnesium). Identifying and managing deficiencies of micronutrients are critical in patients with depression.

#### 8.2.2.12 B Vitamins

B vitamins are a group of eight water-soluble molecules that function as enzymes in metabolic processes.

B vitamins can be found in a wide variety of unprocessed foods. B vitamin deficiency can cause a variety of chronic illnesses, including anemia (vitamin B6: microcytic, vitamins B9 and B12: macrocytic), impairment in peripheral nervous system (vitamins B1 and B12), and severe mental disturbances (vitamins B1, B3, B6, and B12).

Depressive symptoms are a well-known feature of B vitamin deficiency (e.g., B12, B6, and folic acid). Higher intake of vitamin B12 and folate is linked with lower risk of depression; however, it is unclear whether adequate intake of vitamin B12 and folate prevents the onset of depression. Vitamin B12 and folate deficiencies disrupt one-carbon metabolism, resulting in higher homocysteine levels and lower S-adenosyl methionine levels. S-adenosyl methionine is a methyl donor for the rate-limiting step in the synthesis of neurotransmitters (e.g., serotonin, dopamine, and norepinephrine). Lower S-adenosyl methionine levels were frequently reported in patients with depression. Excess homocysteine, on the other hand, causes the production of neurotoxic agents, which overactivate the glutamatergic receptor (N-methyl-D-aspartate). Depression is linked with low levels of B vitamins and/or high levels of homocysteine in general populations. Vitamin B12 has strong correlation with depression in elder populations (Robinson et al. 2011), whereas vitamin B9 is correlated with depression in adult and adolescent populations (Beydoun et al. 2010; Murakami et al. 2010).

Further, either folate or vitamin B12 deficiency contributes to the pathogenesis of MDD by increasing the homocysteine level and causing a vascular response. It is often evident that patients with MDD have lower concentrations of serum or red cell folate. Also, the poor folate status and lower dietary folate are associated with the severity of depression and prolonged episodes of MDD.

#### 8.2.2.13 Antioxidants

The brain requires oxygen for metabolism of various substrates. Due to high PUFA content, the neuronal membranes are vulnerable to lipid peroxidation. In addition to neuronal damage, reactive oxygen species can cause vascular changes through oxidative stress leading to depressive symptoms. Although antioxidants protect the brain from oxidative stress, the antioxidant content of the brain is unusually low. Antioxidant supplementation at high doses prevents the progression of neuronal damage, and thus it could be useful in preventing or treating MDD.

Vitamin C (Ascorbic Acid)

Vitamin C is a potent antioxidant that can help to prevent oxidative stress. High-dose ascorbic acid supplements (3 g/day) may reduce the severity of MDD and depressive scores. Some studies found no link between vitamin A, C, or E intake and the occurrence of depression (Das et al. 2021). Some preliminary data on animal models shows the potential use of ascorbic acid even on depressive symptoms, paving the way not only for its preventive but also therapeutic use (Moretti et al. 2012; Shivavedi et al. 2019).

Vitamin E

Vitamin E is the most important lipid-soluble antioxidant that protects neuronal membranes from peroxidation. Patients with MDD frequently have lower serum vitamin E concentrations than healthy control subjects, and this is also related to the duration of the disease. Some studies, however, found no link between vitamin E and depressive symptoms. The beneficial effects of vitamin E supplementation in MDD may be mediated through neuro-inflammation and oxidative stress modulation.

Selenium (Se)

Selenium is an important modulator of mood. The mechanism by which selenium influences mood is unknown. Selenium is required for the synthesis and metabolism of thyroid hormones. A selenium deficiency affects thyroid hormone metabolism and may be the underlying cause of depressive symptoms. Similarly, selenium deficiency reduces immune function, which is common in MDD patients. Additionally, selenium is needed for the antioxidant enzyme glutathione peroxidase, which protects nerves from lipoperoxidation and tissue damage. The supplementation of 100–150 g selenium/day for 5–6 weeks has significantly improved mood scores.

#### 8.2.2.14 Vitamin D

Vitamin D is a steroid hormone required for calcium absorption and utilization, and bone and mental health. It is synthesized in response to UVB light and is also present in the food chain. To become biologically active, the molecule first undergoes hydroxylation in the liver, followed by a second hydroxylation reaction in the kidneys, brain, and immune system (Borges et al. 2011; Kesby et al. 2011). Vitamin D deficiency is mainly caused by lack of exposure to the sunlight and low vitamin D intake. In vitamin D deficiency, the brain receptors are understimulated, and this may lead to depressive symptoms. A low serum vitamin D level has been linked to depressive symptoms in the majority of cross-sectional studies (Lee et al. 2011).

Further, vitamin D supplementation may affect the inflammatory/oxidative processes among clinical responder subgroup of MDD. At present, there is insufficient evidence for vitamin D supplementation as a monotherapy or adjunct therapy to improve depressive symptoms. Interestingly, a meta-analysis showed positive benefits for adjunctive vitamin D supplementation among patients with major depression (Vellekkatt and Menon 2019) and among people with concurrent major depression and vitamin D deficiency (Vellekkatt et al. 2020).

#### 8.2.2.15 Magnesium

Magnesium is involved in the body's inflammatory defense systems as well as over 300 cellular processes. Magnesium deficiency causes N-methyl-D-aspartate (NMDA) overactivity, which causes depressive symptoms and neuroendocrine changes (Zarate et al. 2013). Serum levels of magnesium are lower in adults with depression. However, the role of magnesium in the prevention of depression is unclear. Furthermore, a healthy dietary pattern is recommended to ensure adequate magnesium intake.

#### 8.2.2.16 Oxidant and Antioxidant

Oxidative stress markers are elevated in patients with depression, while antioxidant markers are low (Liu et al. 2015). Antioxidants found in abundance in fruits and vegetables help in the prevention of depression (Smaga et al. 2015).

#### 8.2.2.17 Gut Microbiota

The gut microbiota may have protective role against inflammation (Ghosh et al. 2020). Whole grains, resistant starch, and vegetables appear to improve the composition of the gut microbiome (Graf et al. 2015; Cebrino and Portero de la Cruz 2020).

#### 8.2.2.18 Trace Minerals

Dietary minerals are elements found in the human body that are necessary for the proper functioning of human body. Macro-minerals are dietary minerals that are abundant in the human body and function as structural (Ca) and electrolyte (Na, K, Cl) minerals. Other dietary minerals exist in trace amounts and serve as enzymic cofactors and cell-signaling molecules. Food sources for dietary minerals vary widely and include animal products (Fe, Ca, P) or vegetarian sources (K, Mg). Mineral toxicity and deficiency can occur in humans. Compared to toxicity, mineral deficiency is common and caused by insufficient intake, excretion, medical

conditions, pregnancy, and lactation. The symptoms differ depending on the mineral and the degree of deficiency.

### Iron

Iron deficiency affects the myelination, cellular and oxidative processes, neurotransmitter metabolism and function, and thyroid hormone metabolism. Reduced brain iron stores have an effect on iron-dependent enzymes that are required for neurotransmitter synthesis, function, and degradation (dopamine, serotonin, and noradrenaline). Iron deficiency in women of childbearing age causes cognitive function deficits such as memory, learning, and concentration. Fatigue, irritability, apathy, and an inability to concentrate are common symptoms of iron deficiency. Also, iron deficiency without anemia is associated with higher depressive scores.

### Zinc (Zn)

Zinc has the highest concentration in the brain after iron. Zinc is necessary for optimal activity of hundreds of intracellular processes (e.g., enzyme cofactors and structure of amino acids). It is localized within synaptic vesicles of specific neurons and modulates synaptic transmission and also acts as a neurotransmitter. It is required in the synthesis of DNA and various regulatory, structural, and enzymatic proteins. Severe deficiency causes immunosuppression and behavioral disturbances such as depression and dysphoria (Maret and Sandstead 2006). Proposed antidepressant mechanisms for zinc include dampening NMDA and glutamatergic hyperactivity, multiple intracellular targets, and complex interactions with the serotonergic system (Nowak et al. 2003). Low levels of Zn are linked with depression among different subgroups of populations (infant, young children, young adult, adultery, elderly, pregnant). In patients with MDD, the blood zinc concentration is lower and correlated with the severity of depression (Swardfager et al. 2013). Supplementation with 25 mg of zinc for 6–12 weeks is used as an adjunct to antidepressant therapy in patients with MDD (Schefft et al. 2017).

### Selenium (Se)

We discussed this under the antioxidant heading.

## 8.3 Potential Mechanism

The mechanisms underlying a possible link between nutrition and depression are unknown; however, it is widely assumed that inflammation plays a role in the pathogenesis of depression (Liu et al. 2016). In addition, the causal mechanisms for various nutrients have been proposed without sufficient evidence (Table 8.3). The B vitamins have no direct effect on the HPA axis or the immune system. B vitamins have an effect on cardiovascular inflammation through the pro-inflammatory amino acid homocysteine (Smulders and Blom 2011). Vitamins B9 and B12 are required for methionine-homocysteine metabolism; methionine is an amino acid required for the translation of protein synthesis. Also, vitamin B6 helps in the condensation of homocysteine into a precursor of the amino acid cysteine (Beydoun et al. 2010; Malouf and Grimley Evans 2003).

## 8.4 Preventive, Protective, and Therapeutic Role of Diet in Depression

Depression may be prevented and treated with nutrition. Therefore, the International Society for Nutritional Psychiatry Research has recommended that nutritional medicine should be considered mainstream in psychiatric practice. "Healthy" dietary patterns are associated with a lower risk of depression (Lassale et al. 2019; Molendijk et al. 2018). However, the observed associations are most likely the result of a number of biological mechanisms. Therefore, research is needed to explore the evidence for underlying mechanism.

### *8.4.1 Dietary Pattern*

Only a limited number of intervention studies have examined the effect of dietary pattern on depression. Also, there is a lack of intervention studies examining the effect of nutrition on depression in different subgroups of population such as middle-aged to older adults. However, the literature suggests that a healthy diet has a beneficial effect on depressive symptoms (Thomas-Brown et al. 2018). The whole-of-diet (or dietary pattern-based) interventions reduced depressive symptoms in a single delivery mode (e.g., red meat intake, selecting lean meat, or following a low-cholesterol diet).

The Supporting the Modification of Lifestyle in the Lowered Emotional States (SMILES) study was the first RCT to evaluate whether improving diet quality improved symptoms of depression in individuals with MDD (Jacka et al. 2017). In this study, participants assigned to dietetic counseling to follow a modified Mediterranean diet had a greater reduction in their depressive symptoms over the

**Table 8.3** Nutrients, dietary sources, and potential mechanism in depression

| Nutrient | Sources | Mechanism of action | Effects of deficiency | Potential mechanism in depression |
|---|---|---|---|---|
| Vitamin B1 (thiamine) | Soymilk, ham, watermelon, acorn squash | Glucose decarboxylation, oxidation, and reduction reactions | Irritability, confusion, apathy | Low levels of vitamin B1 affect the carbohydrate metabolism |
| Vitamin B6 | Fish, meat, poultry, legumes, soy products, bananas | Chemical mediator synthesis; alters NMDA receptors in the brain | Asthenia, irritability, depression | Low levels of vitamin B6 may affect the synthesis of the neurotransmitters (e.g., serotonin, noradrenaline, and dopamine) (Fava and Mischoulon 2009; Miyake et al. 2006) |
| Vitamin B12 | Fish, poultry, meat, milk, fortified soymilk, cereals, and cheese | Works in conjunction with folate in the methionine-synthase-mediated conversion of homocysteine to methionine | Neurological disorders, psychosis, hematological alterations, abnormal peripheral sensation, memory loss, and pain | B vitamin deficiency promotes hyperhomocysteinemia that leads to vascular damage and chronic inflammation. Vascular damage to the carotid and intracerebral arteries can result in low oxygen delivery to the prefrontal cortex, leading to depression (Robinson et al. 2011; Smulders and Blom 2011) |
| Folic acid | Orange, fortified grains, spinach, cereals, broccoli, asparagus, legumes (black-eyed peas and chickpeas) | Methionine-homocysteine metabolism | Megaloblastic anemia, neural tube defects, and mood disturbances | The tetrahydrobiopterin is a cofactor in the synthesis of catecholamines and serotonin. Folate maintains its concentration in brain |
| Vitamin D | Ultraviolet B sunlight, fortified dairy, fatty fish, cereals, eggs, and beef liver | Protection of hippocampal neurons, modulates transport of glucose to the brain | Neuropsychiatric issues, depression | Vitamin D affects both cellular and humoral immune responses (Borges et al. 2011). In addition, vitamin D interacts with HPA axis and affects the hypothalamus function, HPA axis, and production of neurotransmitter |

(continued)

**Table 8.3** (continued)

| Nutrient | Sources | Mechanism of action | Effects of deficiency | Potential mechanism in depression |
|---|---|---|---|---|
| Iodine | Iodized salt, seafood | Major constituent of thyroid hormones, affects gene expression of other hormones and growth factors | Low intelligence, cretinism, hypothyroid-associated depression | It affects thyroid hormone synthesis and gene expression of other hormones and growth factors |
| Selenium | Nuts, meat, and fish | Component of selenoprotein glutathione peroxidase. A selenoprotein glutathione peroxidase is an important antioxidant that is required for thyroid hormone synthesis and metabolism | Low selenium intake associated with poorer mood | The primary function of Se is anti-inflammatory action mediated through the selenoprotein glutathione peroxidase (Duntas 2009). The glutathione peroxidase reduces the COX pathway-mediated production of pro-inflammatory cytokines. Also, it is involved in processing thyroid H2O2, and thus, Se deficiency can cause depressive symptoms by impairing thyroid function (Sher 2001). The Se concentration influences dopamine metabolism (Castaño et al. 1997) |
| Zinc | Red meat, whole grains, and beans | DNA and protein synthesis | Impaired learning, reduced attention; impaired accumulation of PUFA in the body | Two mechanisms:<br>1. Zn affects the balance of pro- and anti-inflammatory cytokines (Prasad et al. 2008)<br>2. Zn changes the productivity of B and T cells and affects the HPA axis (Fraker and King 2004)<br>The neuronal hypotheses suggest that the normal levels of Zn regulate the glutamate release from hippocampal neurons, thus protecting from depression (Szewczyk et al. 2008) |

(continued)

**Table 8.3** (continued)

| Nutrient | Sources | Mechanism of action | Effects of deficiency | Potential mechanism in depression |
|---|---|---|---|---|
| n-3 fatty acids | Fish and other seafood (especially cold-water fatty fish), nuts, seeds, and plant oils | Constituent of cell membranes, substrate for cell-to-cell signal transduction and communication | Impaired sensation, accelerated aging; associated with mood disturbances, dementia, depression | 1. PUFA limits the production of pro-inflammatory eicosanoids and cytokines. Thus, it prevents the inflammatory state leading to clinical depression<br>2. n-3 PUFA helps regulate the production, function, and metabolism of serotonin |

12 weeks. The effects were unrelated to changes in physical activity or body weight but were closely related to the extent of dietary change. The modified Mediterranean diet was based on the Australian Dietary Guidelines and the Dietary Guidelines for Adults in Greece and included recommended servings for 12 food groups: whole grains; vegetables; fruits; legumes; low-fat and unsweetened dairy; raw and unsalted nuts; fish; lean red meats; eggs; chicken; olive oil; and limited intakes of sweets, refined cereals, fried food, fast food, processed meats, and sugary drinks. The type of micronutrient consumed (dietary, supplement, pharmaceutical grade, etc.).

Overall, consumption of more vegetables and fruits and less Western and pro-inflammatory foods lowers the risk of depression. Also, Mediterranean diets, "healthy" diets, and fish consumption may help prevent depression. The International Society for Nutritional Psychiatry Research and the 2015 Dietary Guidelines Advisory Committee report both recommend healthy dietary patterns for the prevention of depression.

## *8.4.2 Macronutrients*

### 8.4.2.1 Proteins

The consumption of milk less than once per day or eating eggs less than once per week was linked to an elevated risk of depression in the National Health and Nutrition Examination Follow-Up Study. Similarly, fewer-than-once-a-week consumption of buttermilk or cheese was linked to a lower incidence of depression. Legumes were the only protein source linked to depression in women. A prospective examination of data from the Women's Health Initiative, on the other hand, found no link between legume consumption and risk of depression. Furthermore, those who consume fish had a lower incidence of depression. Overall, a protein-rich diet is more likely to prevent or protect against depression.

#### 8.4.2.2 Fats

There is mixed evidence regarding the ability of n-3 PUFA to prevent or treat depression.

The higher intake of the omega-3 PUFA, α-linolenic acid, is associated with reduced risk of depression in patients with or without medical comorbidities. Multiple studies have shown the effectiveness of n-3 PUFA supplementation, either as monotherapy or adjuvant treatment (Liao et al. 2019),

In 2010, the American Psychiatric Association and the International Society for Nutritional Psychiatry Research recommended that practitioners should consider n-3 PUFA monitoring and supplementation as the standard of care during the treatment of depression (Freeman et al. 2006). Supplementation with these molecules decreases the levels of key inflammatory cytokines (Adkins and Kelley 2010). Essential fatty acid supplementation has also been shown to improve depressive symptoms in people suffering from treatment-resistant depression. Food sources high in long-chain n-3 fatty acids should be consumed as part of a healthy dietary pattern to help prevent depression. Furthermore, patients with MDD benefited from the addition of n-3 PUFA supplements to antidepressant treatment. Also, the replacement of saturated fats with unsaturated fatty acids, including monounsaturated and polyunsaturated sources, may assist with the prevention and management of depression (Arnett et al. 2019).

#### 8.4.2.3 Carbohydrates

Carbohydrates solely contribute to the dietary glycemic index. Dietary glycemic index has a close association with depression. Evidence suggests a negative correlation of prevalence of depression with intakes of total fiber, vegetable fiber, and breads/cereal fiber (Gopinath et al. 2016). Some recent evidences suggest that it is the dietary glycemic index, not the glycemic load, that is associated with depression (Minobe et al. 2018). Hence, preventive measure should focus in modifying diets as per their glycemic index for a healthy mental well-being.

### *8.4.3 Vitamins and Trace Elements*

#### 8.4.3.1 Vitamins

Higher intake of vitamin B (Gougeon et al. 2016; Skarupski et al. 2010) and vitamin D (Bertone-Johnson et al. 2011) reduces the risk of depression. The outcomes of treatment studies involving vitamins as a preventive and adjunctive therapy for depression have been mixed, depending on the dosage levels used and the health conditions of participants (Fava and Mischoulon 2009; Ford et al. 2008). Folate status affects the antidepressant medication efficacy; specifically, low folate status

appears to attenuate antidepressant response. Unlike folate, vitamin B12 does not appear to alter antidepressant response. Further, the high-level vitamin D supplementation is associated with significant improvement in depressive symptoms (Jorde et al. 2008).

#### 8.4.3.2 Trace Elements

Higher intake of zinc (Das et al. 2021) and total flavonoids (Chang et al. 2016) reduces the risk of depression. Zn as an adjunct to standard antidepressant therapy reduced depressive symptoms and other mood components (e.g., anxiety, fatigue, confusion) in a nonhospitalized population (Nowak et al. 2003).

Se has reported improvement in mood and cognitive function among patients with depression. However, in the majority of studies, the role of Se was investigated in conjunction with other antioxidants (vitamins A, C, and E) (Benton and Cook 1991).

Iron supplementation has improved the depressive symptoms in anemic mothers among South African postpartum women. Furthermore, magnesium supplementation (120 mg/day) has shown to be effective as a monotherapy or adjunct therapy for improving depressive symptoms.

Overall, the adoption of a healthy eating pattern that meets food-based dietary recommendations and nutrient requirements is important to prevent, slow the progression of, or manage depressive symptoms, as well as promote optimal mental and physical health.

## 8.5 Depressive Disorders Among Other Groups

Specific populations may be more vulnerable to nutrient deficiency and may require supplementation to achieve repletion (e.g., vitamin B12 deficiency among vegetarians or vegans, elderly, or pregnant women).

### *8.5.1 Geriatric Depression and Nutrition*

Elderly represents a special population in the eating pattern for many reasons, including reduced hunger and thirst, increased risk of metabolic diseases, increased cravings for sweets, and reduced physical activity (Naitoh and Burrell 1998). This leads to a considerable correlation between the intakes of vitamin B and a decrease in the prevalence of depressive symptoms. Moreover, sufficient nutrient intake of tryptophan derived from diet appears to be an important factor in terms of nutrition and serotonin levels in the body, contrasting depressive symptoms (Klimova et al. 2020). Late-onset depression affects approximately half of the older adults with

depression (Brodaty et al. 2001). Lifestyle changes made at a younger age have an effect on the risk of depression later in life. Dietary recommendations may lower the incidence of depression in this age group.

### 8.5.2 Child and Adolescent Depression and Nutrition

Growing evidence indicates a robust relationship between unhealthy dietary patterns and suboptimal mental health outcomes among children and adolescents. However, due to lack of prospective data, inferences about a causal association between diet and depression in this group should be done with caution. A poor-quality diet may trigger depression by modulating various biological and regulatory mechanisms such as oxidative stress and immune-inflammatory pathways that may predispose to depression among those who are vulnerable. Malnutrition and resultant micronutrient depletions can negatively impact the physical and mental health development of children. Diet and nutrition offer modifiable targets for preventive and therapeutic interventions in this group (Khanna et al. 2019; O'Neil et al. 2014). A recent systematic review confirms as overall there is a strong correlation between healthy dietary patterns or consumption of a high-quality diet and lower depression incidence and severity, and overall better mental health. On the other hand, authors found a connection between unhealthy diet and low-quality diet consumption and depressive symptoms in children (Khalid et al. 2016).

### 8.5.3 Postpartum Depression and Nutrition

Pregnancy represents a peculiar phase in a woman's life, during which healthier lifestyles are generally adopted (e.g., quitting smoking and drinking), hormonal status changes, and diet is modified (food intake of raw and undercooked or uncleaned crustaceans and preserved meat is suspended), with some potential implications to the postpartum phase (Gawlińska et al. 2021). n-3 PUFA depletion occurs during pregnancy and lactation. Maternal stores can drop by half during pregnancy and do not return to prepregnancy levels until 6 months after birth. Postpartum depression is strongly linked with lower rates of seafood consumption and lower concentrations of breast milk DHA (De Vriese et al. 2003).

## 8.6 Limitations of Existing Evidence on Nutrition and Depression

Summarizing the evidence presented hereby, published research indicates that pro-inflammatory diets are associated with an increased risk of depression, and a healthy diet or dietary nutrients may be used to prevent and treat depression. However, the current literature should be interpreted with caution and in light of several limitations listed below.

First, as the majority of studies use a cross-sectional design, it is difficult to establish a cause/effect/comorbid relationship for various nutrients in a longitudinal view. The lack of data from prospective studies with repeated measures makes it difficult to determine the directionality and causality of observations. Second, most of the studies failed to adjust for confounding factors (such as geographic areas, local eating behaviors, smoking, cardiovascular diseases, and personal diet/exercise) and focused on middle-aged or older adults. However, underlying patterns and mechanisms are not consistent across the life span.

Third, the interventional studies are of short duration ($\leq$12 months) and based on participants with specific medical conditions. Furthermore, methodological issues (such as blinding, adherence associated with long-term dietary interventions, expectation bias, and high dropout rates (>30%)) were not adequately addressed. Therefore, evidence is derived from observational studies. Fourth, most studies may have classified depression status inconsistently because it was determined using a variety of depression scales and diagnostic tools, self-report of diagnosis, or antidepressant use rather than a structured diagnostic interview led by an expert clinician. Further, unvalidated tools (e.g., dietary assessment tool, different methods to define dietary patterns) were used to assess diet. Thus, criteria for assessing diet and depression are required for research and clinical decision-making. Fifth, broad-spectrum nutritional interventions have a greater impact than single-nutrient interventions (prescribed diet, nutritional counseling, etc.). Single-nutrient interventions may even be harmful. Finally, it should be considered that.

## 8.7 Future Directions

The varied measures of diet and depression were found in most of the studies, and therefore results are inconclusive and need further investigation. Nowadays, the attention that is paid to the diet and nutritional balance of patients affected by depression is still strongly neglected. More high-quality intervention, cohort studies, studies involving low- and middle-income countries, comparison between different types of diets in distinct areas of the world, and usage of clinical diagnosis of depression are required to increase the robustness and replicability of the studies. This should allow for more detailed analysis and, potentially, more detailed dietary recommendations.

## 8.8 Conclusion

Although there is still insufficient evidence to support nutrient supplementation for the prevention of depressive disorders, some studies indicate that the Mediterranean diet and other healthy dietary patterns may aid in the prevention and management of depression, as well as other severe physical and mental diseases. Furthermore, adequate amounts of vitamins, n-3 essential fatty acids, and trace minerals are required for normal physiological functioning, and the deficiencies of these nutrients are associated with increased risk of depression. Treating these deficiencies often improves depressive disorders. For the future, a more comprehensive therapeutic and clinical approach including knowledge about dietary patterns, specific foods, and biological mechanisms of action of critical nutrients is desirable to develop sound and feasible clinical practice guidelines integrating attention to patients' nutrition.

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