Lead Article

Nutrition and behavioral health disorders: depression and anxiety

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Suboptimal nutrition has been implicated in the underlying pathology of behavioral health disorders and may impede treatment and recovery. Thus, optimizing nutritional status should be a treatment for these disorders and is likely important for prevention. The purpose of this narrative review is to describe the global burden and features of depression and anxiety, and summarize recent evidence regarding the role of diet and nutrition in the prevention and management of depression and anxiety. Current evidence suggests that healthy eating patterns that meet food-based dietary recommendations and nutrient requirements may assist in the prevention and treatment of depression and anxiety. Randomized controlled trials are needed to better understand how diet and nutrition-related biological mechanisms affect behavioral health disorders, to assist with the development of effective evidence-based nutrition interventions, to reduce the impact of these disorders, and promote well-being for affected individuals.

INTRODUCTION

Behavioral health refers to the broad spectrum of behaviors and conditions related to mental and emotional well-being that range from coping with daily challenges of life to behavioral health disorders such as depression, anxiety, and other psychiatric conditions.[1] In 2017, more than 46.6 million adults in the United States reported having a mental illness in the previous year.[2] Thus, strategies are needed for the treatment of behavioral health disorders. In addition, prevention of behavioral health disorders is critical.

Nutrition has a role in the prevention and the treatment of behavioral health disorders.[3] Suboptimal nutrition has been implicated in the underlying pathology of behavioral health disorders because of the essential role of nutrients in the neuroendocrine system. Nutrients, including tryptophan, vitamin B_6, vitamin B_{12}, folic acid (folate), phenylalanine, tyrosine, histidine, choline, and glutamic acid are necessary for production of neurotransmitters such as serotonin, dopamine, and norepinephrine, which are involved in the regulation of mood, appetite, and cognition.[1] Marine-derived omega-3 (n-3) fatty acids regulate dopaminergic and serotoner-

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gic neurotransmission, which can decrease both depression[4] and anxiety.[5] Therefore, poor diet quality leading to inadequate nutrient intake is a risk factor for the development of behavioral health disorders and, accordingly, is a target for the prevention of these illnesses. Furthermore, correction of nutrient deficiencies is important in the management of behavioral health disorders.

The International Society for Nutritional Psychiatry Research has recommended that nutritional medicine be considered mainstream in psychiatric practice, with research, education, policy, and health promotion supporting this novel framework. A challenge to the implementation of this framework is the difficulties in establishing an evidence base, because of the complex multidimensional nature of behavioral health disorders. Numerous risk factors for behavioral health disorders have been identified spanning biological, environmental, social, and intrapersonal factors.[6] Thus, it is difficult to establish the relative contributions of any single factor, and analyses are likely subject to residual confounding. Furthermore, epidemiological investigation of diet and behavioral health disorders is particularly prone to reverse causation; poor diet could be a cause or a consequence of a behavioral health disorder, and, likely, a bidirectional relationship exists. As elegantly described by Begdache et al,[7] mental well-being promotes healthy lifestyle practices (ie, healthy diet, physical activity, and other healthy practices), which then positively reinforce future healthy lifestyle practices. However, the absence of healthy lifestyle practices leads to decreased mental well-being, which, in turn, reduces healthy lifestyle practices, in a vicious cyclic pattern. Therefore, establishing the temporal relationship between diet and behavioral health disorders is complex. Furthermore, intervention studies to establish causative effects of diet on behavioral health are subject to challenges common to clinical nutrition research of any end point,[8] with the added complexity of the lack of objective biomarker outcomes and the reliance on questionnaires and other survey-based methods to determine changes in symptomatology.

The purpose of this narrative review is to describe the global burden and features of depression and anxiety, and summarize recent evidence regarding the role of diet and nutrition in the prevention and management of depression and anxiety.

DIET AND DEPRESSION

Population burden and features of depression

Preventing and managing depressive disorders is a global public health priority because the high prevalence and long duration creates substantial economic, personal, and health care burdens. Since 1990, major depressive disorders have been the second greatest contributor to global disease burden quantified as years of life lived in less than ideal health.[9] In 2017, 13.3% of youths aged 12 to 17 years and 7.1% of adults aged older than 18 years had a major depressive episode.[2] Depressive disorders include major depressive disorder, dysthymia, and bipolar disorder, each of which causes significant impairments in the ability to function in everyday life. These severe illnesses, which are associated with increased risk for suicide, need to be distinguished from normative and transient minor symptoms of depression.[10] Symptoms of major depression include low mood, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, feelings of tiredness, poor concentration, and thoughts of suicide.

Depressive disorders are complex and have no single cause. Sex, gender, socioeconomic status, social support, stress, alcohol and drug use, genetic and epigenetic factors, inflammation, medical illnesses, endothelial dysfunction, and diet all contribute to increased risks.[11,12] Emerging evidence suggests the microbiome is associated with the development of depression; however, causative links have yet to be established.[13–16]

Dietary patterns and depression

Diet is a modifiable risk factor for depression; thus, improvements to diet may reduce the burden of depressive disorders. Of interest is that the increase in depressive disorders over the past decades[2] parallels a decline in healthy lifestyle behaviors, including poorer diet quality.[17]

Clinical trial evidence for the effect of dietary patterns on depression. Several clinical trials have assessed whether changes in dietary patterns affect depressive symptoms. The most recent systematic review and meta-analysis, including 16 randomized controlled trials (RCTs) and data for 45826 nonclinically depressed participants, reported whole-of-diet (or dietary pattern–based) interventions reduced depressive symptoms (Hedges' g, 0.28; 95%CI, 0.10–0.45; $P = 0.002$) compared with the control condition (active and nonactive).[18] Similarly, a systematic review of RCTs, including predominantly nondepressed participants, that evaluated interventions that used a whole-diet (or dietary-pattern) approach reported that 8 of 17 studies observed significant improvements in depression scores compared with the control group, with small to very large effect sizes observed (Cohen *d*, 0.19–2.02).[19] In this review, studies that reported a significant improvement in depression

with the dietary intervention were similar in that they used a single delivery mode, had a qualified dietitian deliver the intervention, and were less likely to recommend reducing red meat intake, selecting lean meat, or following a low-cholesterol diet. Since the review was conducted, several RCTs have continued to investigate dietary approaches to reducing depressive symptoms.

The Supporting the Modification of lifestyle in Lowered Emotional States (SMILES) study was the first RCT to explicitly evaluate whether improving diet quality improved symptoms of depression in individuals who met criteria for a major depressive episode and low diet quality.[20] Participants who were randomly assigned to dietetic counseling to follow a modified Mediterranean diet had a greater reduction in their depressive symptoms over the 12-week period compared with those in the social support group. The effects were independent of changes in physical activity or body weight, and closely related to the extent of dietary change. That is, those who improved their diet the most experienced the greatest benefit to their depression. 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; fruit; 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. Similarly, in a RCT of adults with self-reported depression, a Mediterranean-style dietary intervention that included food hampers, cooking classes, and fish oil supplementation (900 mg/d docosahexaenoic acid [DHA] and 200 mg/d eicosapentaenoic acid [EPA]) improved adherence to the Mediterranean diet, reduced depression, as measured by the Depression Anxiety Stress Scale, and improved mental health quality-of-life scores, compared with a control group that attended social support sessions, after 3 months.[21] This intervention was also highly cost-effective in terms of cost per case of major depression resolved.[22] An analysis from the Prevención con Dieta Mediterránea (PREDIMED) study showed that individuals with type 2 diabetes randomly assigned to the Mediterranean diet with nuts were 41% less likely to be diagnosed with depression during follow-up compared with the control group (hazard ratio, 0.59; 95%CI, 0.36–0.98).[23]

Other healthy dietary patterns, such as the Dietary Approaches to Stop Hypertension (DASH) diet, have also improved depressive symptoms. The DASH diet is high in fruits, vegetables, and low-fat dairy, and low in saturated fat. In a secondary analysis of a study of postmenopausal women (n = 95) who generally did not report depressive symptoms at baseline (n = 8 reported a mental health condition and/or took medication for a mental health condition at baseline), a low-sodium (~1600 mg/d) DASH diet containing daily servings of lean meat reduced depression and anger scores in comparison to a diet that was lower in fruits and vegetables and lean meat, after 14 weeks.[24] Collectively, these studies suggest that a healthy dietary pattern consistent with current dietary recommendations that includes vegetables and fruits, seafood, olive oil, nuts, and grains may improve depressive symptoms in nondepressed and clinically depressed individuals.

Epidemiological evidence relating dietary patterns to depression. The available epidemiological evidence on dietary patterns and depression is generally consistent with the findings of RCTs suggesting that healthy dietary patterns are associated with less depressive symptoms. Epidemiological analyses add insights into the relationship between diet and depression by examining the dietary predictors of incident depression. The association between dietary patterns and depression has been reported in more than 50 studies conducted in many countries with varying definitions of healthy dietary patterns.

A systematic review and meta-analysis of prospective cohort studies showed that greater adherence to healthful dietary patterns including healthy/prudent, Mediterranean, pro-vegetarian (ie, higher in plant foods relative to animal foods), and Tuscan was associated with a 23% lower odds of depression (overall odds ratio [OR], 0.77; 95%CI, 0.69–0.84). A dose-response linear relationship was noted, whereby a lower incidence of depression was observed with increasing diet quality.[25] In the analysis by Molendijk et al,[25] all the included studies adjusted for age and sex; 16 also adjusted for socioeconomic status. Their findings are supported by previous meta-analyses, including a pooled analysis of 9 observational studies in which high adherence to a Mediterranean dietary pattern was associated with a 32% relative risk (RR) reduction for depression (RR, 0.68; 95%CI, 0.54–0.86); moderate adherence was associated with a 23% RR reduction for depression (RR, 0.77; 95%CI, 0.62–0.95).[26] Similarly, a meta-analysis of 13 epidemiological studies showed that in community-dwelling cohorts, healthy dietary patterns were associated with a 16% reduction in the risk of depression (OR, 0.84; 95%CI, 0.76–0.92).[27] These healthy dietary patterns were characterized by high intakes of fruits, vegetables, fish, and whole grains. In agreement, authors of the most recent comprehensive review of large and well-conducted longitudinal cohort studies concluded that reduced risk of depression was associated with dietary patterns emphasizing seafood, olive oil, vegetables, fruits, and nuts.[28]

Vegetarian dietary patterns have been associated with increased[29–34] and decreased[35] risk of depression and mental disorders. Furthermore, low levels of meat consumption have been related to increased risk of depression in cross-sectional analyses.[36–38] However, a meta-analysis published in 2017 reported no association between meat consumption and depression prevalence when data from 6 cross-sectional analyses were pooled (OR, 0.89; 95%CI, 0.65–1.22), but higher meat consumption was associated with increased depression incidence in a pooled analysis of 3 prospective cohort studies (RR, 1.13; 95%CI, 1.03–1.24).[39] The lack of concordance observed between these studies is likely because of residual confounding, reverse causation, the absence of nutrient-status assessment, and the heterogeneity in how meat consumption is defined and measured. Increased risk of depression with vegetarian and vegan diets is biologically plausible because vegetarians and vegans are at higher risk for suboptimal intake of essential nutrients such as vitamin B_{12}, iron, and n-3 fatty acids,[40] which are required for optimal functioning of the neuroendocrine system.[1,41] An appropriately planned vegan or vegetarian diet will meet nutrient requirements[40]; however, without adequate planning, nutrient deficiencies may manifest. The current evidence base is limited by the inconsistencies in the definition of vegetarian diets used across studies, a lack of distinction between meat types and processing, and seldom assessment of the nutrient adequacy of vegetarian or vegan diets and whether this is a mediating factor. Thus, additional research using interventional and/or prospective designs is required to establish whether vegetarian or vegan diets are causatively associated with depression; however, in the meantime, it is pertinent to ensure that if a vegan or vegetarian diet is chosen, it is appropriately implemented to ensure nutrient requirements are met.[40]

In total, evidence from clinical trials and epidemiological research suggests a healthy dietary pattern may reduce depression symptoms in depressed and nondepressed individuals. Furthermore, observational research shows healthy dietary patterns are associated with a lower risk of depression. However, it should be acknowledged that depressive disorders can result in poorer diet; thus, the inability to determine directionality is a significant limitation of observational research in the context of behavioral health disorders. Nevertheless, the reviewed evidence is consistent with the conclusions of the 2015 Dietary Guidelines Advisory Committee report[42] and a publication by members of the International Society for Nutritional Psychiatry Research that recommends healthy dietary patterns for the prevention of depression.[43]

Macronutrients and depression

This section summarizes findings from clinical trials and epidemiological studies examining how macronutrient intake relates to depression and depressive symptoms, with a focus on total dietary macronutrient composition. Intake of a single macronutrient cannot be changed in isolation, because a change in intake of 1 macronutrient results in a proportional shift in intake of another macronutrient(s). Thus, examination of the relationship between single macronutrients and health outcomes often yields inconsistent results because of a dependence on the macronutrient replacement. However, although this approach is relatively standard in studies of blood lipid and lipoprotein levels and cardiovascular outcomes, it is less commonly applied to the study of depression, which limits our understanding of how macronutrient composition modulates depressive symptoms and depression.

Clinical trial evidence for the effect of macronutrient composition on depression. Few clinical trials have examined how dietary macronutrient composition affects depressive symptoms. The available data are from trials of nondepressed individuals consuming weight-loss diets differing in the macronutrient composition; therefore extrapolation of results to prevention or management of depression in free-living populations is limited although relevant to contexts where nondepressed individuals are engaging in weight loss.

Overall, the data show that depressive symptoms are not affected by diets of differing macronutrient composition but are generally improved by weight-loss diets (regardless of the macronutrient composition).[44] In a 12-month, randomized, parallel trial of nondepressed adults with overweight or obesity, differences were observed in depressive symptoms after a moderately energy-restricted, very-low-carbohydrate diet (carbohydrate, 4% kcal; protein, 35% kcal; fat, 61% kcal [saturated fatty acid (SFA), 20%; other fatty acids, not reported]) compared with a moderately energy-restricted, low-fat diet (carbohydrate, 46% kcal; protein, 24% kcal; fat, 30% kcal [SFA, <8% kcal]).[45] At 12 months, compared with the low-fat group, the very-low-carbohydrate group had higher scores for the Profile of Moods State Questionnaire Anger-Hostility and Depression-Dejection subscales and a higher total mood disturbance score; no differences were observed in the Beck Depression Inventory. In this study, initial improvements in these scores were observed with both diets, but the very-low-carbohydrate group returned to baseline values. In a comparable 12-month, randomized, parallel trial of nondepressed adults with type 2 diabetes, no differences in depressive symptoms,

measured every 4 weeks during the intervention period using the Beck Depression Inventory Score and the Profile of Moods State Questionnaire, were observed with an energy-restricted, low-carbohydrate (carbohydrate, 14% kcal; protein, 28% kcal; fat, 58% kcal [monounsaturated fatty acids, 35% kcal; polyunsaturated fatty acids [PUFA], 13%; SFA, <10% kcal]) vs an energy-restricted, high-carbohydrate diet (carbohydrate, 53% kcal; protein, 17% kcal; fat, 30% kcal [monounsaturated fatty acids, 15% kcal; PUFA, 9%; SFA, <10% kcal]).[46] In the 2 trials by Brinkworth et al,[45,46] similar weight loss was achieved in the comparison groups regardless of the macronutrient differences.

The discordant results are likely explained by the restrictive carbohydrate target (4% kcal) imposed in the study of adults with overweight or obesity[45] that may have been harder to maintain long term than the carbohydrate target (14% kcal) in the study of individuals with type 2 diabetes,[46] resulting in regression to baseline values. In addition, the intervention used in the study of individuals with type 2 diabetes[46] included an intensive, planned, supervised exercise program, whereas in the study of overweight/obese adults,[45] no recommendations for exercise were given. Because exercise is associated with the alleviation of depressive symptoms, exercise may have blunted any potential diet-induced effects. These studies suggest that in the context of hypocaloric diets, macronutrient composition has limited deleterious effects on depressive symptoms in nondepressed individuals. Furthermore, clinical research is required to examine how the macronutrient composition of weight-maintenance diets affects depressive symptoms in individuals who are depressed.

Another consideration is macronutrient quality, specifically that of dietary carbohydrates. In a 2-period, randomized, crossover, controlled-feeding study, the effect of high and low glycemic-load diets (carbohydrate, 55%; protein, 15%; fat, 30%) on depressive symptoms were examined in nondepressed individuals.[47] After 4 weeks, compared with the low glycemic-load diet, the Profile of Moods State Questionnaire subscales including Fatigue-Inertia and Total Mood Disturbance scores were higher after the high glycemic load diet, as was the Center for Epidemiological Studies Depression Scale score. The low glycemic-load diet increased the Vigor/Activity subscale of the Profile of Moods State Questionnaire relative to the high glycemic-load diet. This study suggests a high glycemic-load diet may trigger total mood disturbances, higher levels of fatigue, and depressive symptoms relative to a lower glycemic-load diet. Only 1 other clinical trial, to our knowledge, has examined how dietary glycemic index/load affects depressive symptoms;[48] however, the macronutrient composition of the test diets was not matched and the interventions differed beyond glycemic index/load, limiting comparativeness. This study reported no differences in depressive symptoms, measured by the Center for Epidemiological Studies Depression Scale, in nondepressed individuals with poorly controlled type 2 diabetes following an American Diabetes Association diet vs a low glycemic index diet.[48] Additional research is required to confirm the findings of Breymeyer et al[47] and to examine the longer-term effects in populations with and without depression. In the meantime, whole-grain carbohydrate sources should be chosen in place of refined carbohydrates, a recommendation consistent with current dietary guidance.[49]

The physiological effect of fatty acids differ by type[50,51]; however, clinical trial evidence for the effect of fatty acids by saturation level on depressive symptoms and depression is not available. There are substantial commonalities in risk factors for depression and cardiovascular disease, including inflammation and endothelial dysfunction; therefore, dietary recommendations for cardiovascular disease prevention may be appropriate for depression prevention and management. Replacement of saturated fats with unsaturated fatty acids, including monounsaturated and polyunsaturated sources, as recommended in the 2015–2020 Dietary Guidelines for Americans and CVD Prevention Guidelines from the American College of Cardiology, American Heart Association, and the National Lipid Association may assist with the prevention and management of depression,[49,52–54] although research is needed to confirm this.

Several clinical trials have examined the effect of n-3 PUFA supplementation on depression. For prevention of depression, the totality of the evidence shows that food sources rich in long-chain n-3 fatty acids should be consumed as part of a healthy dietary pattern; n-3 supplements are not recommended for depression prevention.[43] For management of depression, a meta-analysis of 10 RCTs including 402 patients showed benefit of the addition of n-3 PUFA supplements to antidepressant treatment in patients with major depressive disorder (standardized mean difference, -0.48; 95%CI, –0.84 to –0.11).[55] The 2010 American Psychiatric Association Practice Guideline for the Treatment of Patients With Major Depressive Disorder states that n-3 fatty acids are generally recommended as an adjunctive therapy for major depressive disorders.[56] This is consistent with the recently published recommendations of an expert subcommittee of the International Society for Nutritional Psychiatry Research.[57]

Epidemiological evidence relating macronutrient composition to depression. A relatively limited number of observational studies have examined how dietary

macronutrient composition relates to depression, and there have been few attempts to account for interrelations between macronutrients. The available data show total carbohydrate consumption is not prospectively associated with incident depression in postmenopausal women after adjustment for potential confounders, including other macronutrients[58]; prospective evidence from other populations is lacking. An analysis of the National Health and Nutrition Examination Follow-Up Study showed that higher protein intake (in grams) at baseline was associated with lower risk of severely depressed mood in men (RR, 0.38; 95%CI, 0.16–0.92) after simultaneous adjustment for total energy intake and inter-correlations between macronutrients and other potential confounders, after 10.6 years of follow-up.[59] No association was detected between percentage of energy from protein and severely depressed mood in men in a fully adjusted model. In contrast, in women, protein intake (in grams) was not associated with severely depressed mood (RR, 0.92; 95%CI, 0.48–1.78), but a higher percentage of energy from protein was associated with increased RR of severely depressed mood (RR, 2.47; 95%CI, 1.24–4.90).[59] The reasons for these conflicting observations with protein intake in grams vs percentage of total energy in men and women are unclear but may be because dietary intake was only measured at baseline, increasing the likelihood of misclassification, or protein sources may differ in men and women. Finally, in a cross-sectional study of male Japanese workers at a manufacturing company, no association was observed between intake of protein, fat, or carbohydrate and depressive symptoms in models unadjusted and adjusted for potential confounders, including intakes of other macronutrients.[60] Thus, heterogeneity exists in how macronutrients prospectively or cross-sectionally associate with depression, which is likely because of the substantial variation in food sources of macronutrients.

In studies that examined the correlation between major contributors to overall intake of a given macronutrient and depression, greater consistency in findings is observed. For example, prospective cohort studies have shown greater intake of added sugars from sugar-sweetened beverages and sweet foods is associated with higher depression risk.[61–63] In a meta-analysis of 4 prospective cohort studies, highest vs lowest consumption of sugar-sweetened beverages was associated with an increased risk of depression (RR, 1.30; 95%CI, 1.19–1.41).[64] Hu et al[64] also reported a nonlinear dose-response relationship whereby, compared with nonconsumption, 2 cups/d of sugar-sweetened beverages increased the RR of depression by 5% and 3 cups/d increased the RR by 25%. Similar results were reported in a prospective analysis of the Women's Health Initiative cohort, in which higher intake of added sugars (OR, 1.23; 95%CI, 1.07–1.41), but not total sugars (OR, 0.99; 95%CI, 0.83–1.18) or total carbohydrate (OR, 0.97; 95%CI, 0.77–1.22) intake, was associated with higher odds of incidence depression after 3 years of follow-up.[58] Higher intake of fiber (OR, 0.86; 95%CI, 0.76–0.98) was associated with lower risk of incident depression in this cohort. Together, these prospective analyses suggest carbohydrate quality may be more strongly associated with depression risk than total carbohydrates per se.

This finding is supported by a prospective analysis of the Seguimiento Universidad de Navarra Spanish Cohort that showed an inverse association between the Carbohydrate Quality Index (a measure of intake of higher-quality carbohydrates) and depression; the highest tertile of the Carbohydrate Quality Index was associated with a 30% RR reduction for depression.[62] Interestingly, in this cohort, no association was observed between dietary glycemic index and depression, although glycemic index is not a reliable proxy for the glycemic response to carbohydrate intake,[65,66] which may explain this finding. A recent systematic review and meta-analysis of 5 cross-sectional studies showed no association between dietary glycemic index or dietary glycemic load and depression.[67] However, in a prospective analysis from the Women's Health Initiative Cohort, higher dietary glycemic index was associated with increased odds of incident depression after 3 years of follow-up (OR, 1.22; 95%CI, 1.09–1.37); higher dietary glycemic load was not associated with incident depression (OR, 1.01; 95%CI, 0.82–1.24).[58] This discordance is likely because the glycemic-load calculation includes the glycemic index of foods consumed as well as total carbohydrate intake, and, as previously described, carbohydrate intake per se is not associated with depression risk. Between-study heterogeneity in the observed relationships between glycemic index and glycemic load is likely because of variation in food sources consumed by these cohorts and the limitations of the glycemic index and load calculations to predict glycemic response. The findings suggest that diets high in added sugars and refined carbohydrates may increase risk of depression; however, higher consumption of fiber may be protective.

There has been limited investigation of how protein sources associate with depression risk. In a cross-sectional study of male Japanese workers at a manufacturing company, plant protein intake was associated with lower odds of depression after adjustment for age and worksite (OR, 0.67; 95%CI, 0.50–0.89), although after adjustment for potential confounders, including intake of energy, folate, vitamins B_6 and B_{12}, magnesium, iron, and PUFA, no associations were

observed between intake of plant or animal protein and depressive symptoms.[60] A prospective analysis of Italian adults found higher intake of fish/shellfish was associated with a decrease in depressive symptoms, after adjustment for potential confounders, over 9 years of follow-up; no associations were observed for intake of dairy products, nuts/legumes, or red or processed meat.[68] Notably, in this cohort, Elstgeest et al[68] also examined the potential for bidirectional associations by examining depressive symptoms as the exposure and sources of protein intake as the outcome and found that greater depressive symptoms were associated with a reduction in red or processed meat and an increase in dairy intake. Thus, the lack of prospective association between red or processed meat intake and dairy intake suggests exposure to these protein sources is not associated with increased risk of depressive symptoms, but the finding that individuals with more depressive symptoms had reduced consumption of red or processed meat and higher intake of dairy suggests intake modification because of depression rather than intake being related to development of depressive symptoms. This also highlights the potential for reverse causality to explain the results of observational analyses, especially in nonprospective studies and those without repeated assessment of dietary exposure.

In an analysis from the National Health and Nutrition Examination Follow-Up Study, consumption of milk less than once per day at baseline was associated with a doubling in RR of depression during the 10.6 years of follow-up in men, after adjustment for total energy intake and other potential confounders; no association was detected in women.[59] In this study, compared with daily consumption of eggs, eating eggs less than once per week was associated with a 60% lower risk of depression in men. Similarly, consumption of buttermilk or cheese less than once per week was associated with a 44% lower risk of depression in men. No associations were detected between depression and intake of meat/poultry, fish/seafood, or legumes in men this cohort. In women, the only protein source associated with depression was legumes, such that compared with consumption 3 or more times per week, intake fewer than 1 time per week was associated with a 35% lower risk of depression. In contrast, a prospective analysis of data from the Women's Health Initiative showed no association between intake of legumes and risk of incidence depression.[58] The lack of data from prospective analyses with repeated measures of dietary exposure makes it difficult to determine the directionality of observed associations between protein consumption and depression. Thus, additional research in this area is required.

Few epidemiological studies have examined how intake of dietary fat sources relates to depression. A meta-analysis of 26 observational studies involving 150278 participants found that the RR of depression was approximately 27% lower among those comsuming the most fish; however, large between-study heterogeneity was observed in the frequency of fish consumption.[69] In a subsequent meta-analysis of 31 studies including 255076 individuals, higher intake of fish, EPA plus DHA, and total n-3 PUFA was associated with lower risk of depression.[70] For fish consumption, 50 g/d was associated with a 16% reduction in depression (RR, 0.84; 95%CI, 0.72–0.99) compared with no consumption. Furthermore, a dose-response relationship was observed for total n-3 PUFA intake, and compared with 0, 0.5, 1, 1.5, and 1.8 g/d, reduced the risk of depression by 31%, 52%, 67%, and 70%, respectively. For EPA plus DHA, a similar dose-response relationship was observed. A meta-analysis of 14 case-control studies examining blood levels of n-3 fatty acids found lower levels of EPA, DHA, and total n-3 PUFA in patients with depression compared with control participants.[4]

In summary, clinical trials examining how dietary macronutrient composition affects depressive symptoms are limited to nondepressed adults undergoing weight loss and show limited effects of varying fat, protein, and carbohydrate intake on depressive symptoms. Epidemiological investigations of depression and macronutrient intake have largely ignored macronutrient inter-relatedness, limiting the generalizability of the findings. However, epidemiologic studies show some consistency in the observed relations between dietary sources of macronutrients and depression. These analyses suggest intake of added sugars and refined carbohydrates is positively associated with depression; however, higher consumption of fiber, fish, and n-3 fats may be protective.

Micronutrients and depression

Micronutrients are involved in metabolic pathways that affect the development and optimal functioning of the nervous system. Thus, inadequate intake may adversely affect psychological status, thereby increasing risk of depressive disorders. Micronutrients associated with mental status include the B vitamins folic acid, vitamin B_6, and vitamin B_{12}, and vitamin D. In addition, zinc and magnesium have been implicated in mental health status. Identifying and managing deficiencies in essential fatty acids, magnesium, zinc, B vitamins (folate, B_{12}), and vitamin D is critical in individuals with depression.

B vitamins Depression has long been recognized as a symptom of deficiency of B vitamins, including folic

acid/folate, B_6, and B_{12}.[71] Deficiencies in vitamin B_{12} and folate affect 1-carbon metabolism, causing elevations in homocysteine and lower *S*-adenosyl methionine levels.[72] *S*-adenosyl methionine is a methyl-donor in the rate-limiting step in the synthesis of serotonin, dopamine, and norepinephrine,[73] and lower *S*-adenosyl methionine levels have been documented in depressed vs nondepressed individuals.[74] Excessive homocysteine also leads to the production of neurotoxic agents, which overactivates the glutamatergic receptor (*N*-methyl-D-aspartate), and is implicated in depression.[75]

Higher intake of vitamin B_{12} and folate is associated with lower risk of depression in epidemiological studies,[76,77] although it is unclear whether vitamin B_{12} and folate adequacy prevents the onset of depression. Randomized clinical trials show folate and/or vitamin B_{12} supplements do not reduce depressive symptoms in individuals without depressive symptoms,[71] and supplementation is not recommended for prevention in replete adults.[43] There is the potential for vitamin B_6 to be neurotoxic and folic acid/folate supplementation to mask a vitamin B_{12} deficiency; thus, daily supplementation with these vitamins is not recommended for the general population. Consumption of a healthy dietary pattern will ensure adequate vitamin B_{12} and folate intake. For treatment of depression, systematic reviews and meta-analyses of RCTs have found no clinical benefit of folate, vitamin B_6, or B_{12} supplementation as an adjunct to antidepressant treatment for depressive symptoms.[55,78]

Vitamin D. Vitamin D is synthesized in response to sunlight and is present in the food supply. Vitamin D is required for the absorption and utilization of calcium, and maintenance of bone health. Lack of exposure to the sun, as well as low vitamin D intake, results in vitamin D insufficiency with subsequent consequences on mental health. Specifically, vitamin D receptors located in the brain are understimulated when vitamin D is insufficient and this may lead to depressive symptoms.[79,80]

A meta-analysis of 7 RCTs with 3191 participants found that vitamin D supplementation was associated with neither benefit nor worsening of depressive symptoms; however, a subgroup analysis showed that in 2 trials of patients with clinically significant depression or major depressive disorder, a moderate, but statistically significant, benefit of vitamin D supplementation on depressive symptoms was observed.[81] Nevertheless, at present, there is insufficient evidence for vitamin D supplementation as a monotherapy or adjunct therapy to improve depressive symptoms.[56]

Magnesium. Magnesium is involved in more than 300 cellular processes, including inflammatory defense systems. Magnesium depletion leads to *N*-methyl-D-aspartate overactivity and, as a consequence, to depressive symptoms, neuroendocrine changes, sleep disturbances, and increased inflammation.[82] Serum levels of magnesium are lower in adults with depression vs nondepressed control study participants; however, data are mixed with regard to the relationship between magnesium intake and depression.[83,84] Although the role of magnesium in the prevention of depression is unclear, it is prudent to ensure adequate intake of magnesium with a healthy dietary pattern. Magnesium was identified as a shortfall nutrient by the 2015 Dietary Guidelines Advisory Committee because it is underconsumed by the US population,[42] underscoring the importance of adequate intake.

Clinical trials of magnesium supplementation for management of depression have yielded mixed results. A recent randomized, double-blind, placebo-controlled trial of patients ($n = 37$) with recurrent depressive disorders showed that supplementation of 120 mg/d of magnesium aspartate plus the antidepressant fluoxetine had no effect on depressive symptoms compared with the placebo plus fluoxetine after 8 weeks.[85] At present, there is no clear evidence for magnesium supplementation as monotherapy or adjunct therapy to improve depressive symptoms.[86]

Zinc. Zinc is necessary for optimal activity of hundreds of intracellular processes, and severe deficiencies result in neurological disorders and symptoms common to depressive disorders, including immune dysfunction, irritability, mood changes, and cognitive impairments. Proposed antidepressant mechanisms for zinc include dampening *N*-methyl-D-aspartate and glutamatergic hyperactivity, and complex interactions with the serotonergic system and multiple intracellular targets.[87] Lower levels of zinc among people with major depressive disorders have been reported in systematic reviews.[88]

Few RCTs have examined the effect of zinc on depression.[89] A recent meta-analysis of 3 RCTs showed supplementation with 25 mg of zinc for 6–12 weeks as an adjunct to antidepressant therapy had a favorable effect on depressive symptoms in patients with major depressive disorder.[55] Additional research is required to establish whether zinc is an effective adjunct therapy in patients with depressive disorders who are zinc replete.

Summary recommendations on diet and depression

Current evidence does not support nutrient supplementation for the prevention of depressive disorders, but

relatively convincing data from RCTs and prospective cohort studies suggest the Mediterranean diet and other healthy dietary patterns may assist in the prevention of depressive illnesses and potentially in the management of depression. These dietary patterns emphasize seafood, olive oil, vegetables, fruits, nuts, lean protein sources, whole grains, and vegetable oils, and limit nutrient-poor, energy-dense foods high in added sugars and saturated fats, including sugar-sweetened beverages, pastries, and refined grains. Healthy dietary patterns include adequate amounts of n-3 essential fatty acids, vitamin B_{12}, magnesium, and zinc required for normal physiological functioning, and because suboptimal intake of these nutrients has been associated with increased risk of depression, deficiencies should be treated. Specific populations may be more vulnerable to nutrient deficiency and may require supplementation to achieve repletion (eg, vitamin B_{12} deficiency among vegetarians or vegans and the elderly). 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 health.

DIET AND ANXIETY

Population burden and features of anxiety.

Several anxiety disorders are characterized by persistent, excessive, and unrealistic worry about everyday occurrences, and are based on criteria defined in the *Diagnostic and Statistical Manual of Mental Disorders*.[10] The spectrum of anxiety disorders is not 1 particular disorder; it clusters around excessive, irrational fear and dread. Approximately 31.1% of the US population has experienced an anxiety disorder in their lifetime; prevalence is 2-fold higher in women compared with men.[90] The prevalence of anxiety disorder is highest from childhood through middle age.[10]

Evidence has shown that nutrition, including dietary patterns, foods, and individual nutrients affect anxiety. Key nutrients (eg, B vitamins, vitamin C, magnesium, and zinc) regulate stress responses via involvement in the production and metabolism of neurotransmitters, including serotonin, noradrenaline, and dopamine. Chronic stress may decrease synthesis of neurotransmitters, which may increase the risk of severe anxiety.[91] Nutrients also affect neuronal membrane structure and neurotransmitter release.[92] In addition, B vitamins, vitamin C, magnesium, and zinc are involved in the conversion of α-linolenic acid to longer-chain n-3 fatty acids; n-3 fatty acids are associated with lower risk of anxiety. These findings provide a plausible explanation for how nutrition can affect anxiety.

DIETARY PATTERNS AND ANXIETY

Clinical trial evidence for the effect of dietary patterns on anxiety.

Few RCTs of dietary interventions have been conducted to examine how dietary patterns affect anxiety. Opie et al[19] conducted a systematic review of RCTs to examine the effectiveness of whole-of-diet or dietary pattern–based approaches for the treatment of anxiety. They identified 10 studies that measured anxiety, and of these studies, 2 reported improvements in anxiety with the intervention; however, both of these studies included concurrent recommendations for other lifestyle factors, including physical activity and smoking cessation. Since the publication of the systematic review by Opie et al,[19] the SMILES RCT demonstrated that individual nutrition counseling to follow a modified Mediterranean dietary pattern reduced anxiety (for Hospital Anxiety and Depression Scale–anxiety, Cohen *d*, -0.594; 95%CI, –1.147 to –0.042) in individuals with moderate to severe depression compared with social support.[20] However, a recent systematic review and meta-analysis of 11 RCTs (n = 2270) showed no effect of dietary interventions on anxiety.[18] Therefore, heterogeneity exists in the results of clinical trials investigating the effect of dietary patterns on anxiety, likely because many of the studies did not include participants with clinical levels of anxiety making it harder to detect effectiveness; additional research is needed.

Epidemiological evidence relating dietary patterns to anxiety.

Although there has been limited investigation of dietary patterns and anxiety in clinical trials, the relationship between dietary patterns and anxiety has been studied in epidemiological studies from diverse countries worldwide. These observational analyses have focused on dietary patterns including traditional (ie, one that has a historical country lineage to long-standing agrarian production practices), modern, Mediterranean, vegetarian, and Western.[93–99] Traditional dietary patterns in Australia (characterized by vegetables, fruit, meat, fish, and whole grains),[95,100] China[100] (characterized by "a typically healthy and recommended diet," and included foods such as gruel, oatmeal, whole grains, fresh yellow or red vegetables, fruit, and soy milk),[100] and the Mediterranean[95] have been associated with a lower risk for anxiety disorders. In a prospective analysis from a large clinical trial

conducted in Spain, the PREDIMED study, increased symptoms of anxiety were associated with a lower Mediterranean diet score.[101] A healthy diet score was inversely related to anxiety in women in Norway.[102] There is also evidence that greater adherence to a lacto-vegetarian dietary pattern is associated with decreased odds of anxiety.[96] In addition, anxiety scores were lower in men who reported consuming a vegan diet, and daily fruit and vegetable consumption.[103] Thus, the findings of epidemiological studies suggest high-quality dietary patterns, which contain adequate amounts of nutrients known to be associated with anxiety, may reduce the risk of anxiety.

Some dietary patterns are associated with increased risk of anxiety in cross-sectional analyses. A Western dietary pattern consisting of processed or fried foods, refined grains, sugary foods, and beer is associated with more psychological symptoms.[100] Authors of a cross-sectional study conducted in Australia reported that individuals with more severe anxiety consumed a diet with less variety, fewer healthy food choices, fewer fruits and vegetables, and more nutrient-poor, energy-dense foods.[104] Similarly, in a cross-sectional study conducted in Iran, a Western dietary pattern was associated with an increase in anxiety, and there was a trend toward greater risk of psychological stress with consumption of a fast-food dietary pattern among women.[96] Another cross-sectional study in Iran showed that increased consumption of processed food was associated with anxiety.[93] In a cross-sectional study conducted in China, participants in the highest tertile of snack consumption had the highest risk of anxiety (without depression).[98] In addition, high consumption of animal foods was associated with a greater risk of psychological symptoms. Authors of a cross-sectional study conducted in Greece reported that high consumption of sweets and meat and meat products was associated with higher anxiety scores in women.[99] These cross-sectional studies from diverse populations suggest poorer-quality dietary patterns are related to increased anxiety risk.

Based on epidemiological studies conducted in many different countries, a healthy dietary pattern characterized by fruits and vegetables, whole grains, lean protein sources, nuts, and legumes, and low in added sugars may lower the risk of anxiety disorders. In contrast, a Western-style dietary pattern that does not meet food-based dietary recommendations is associated with greater risk of anxiety.

In summary, higher diet quality is associated with reduced risk of anxiety, although additional RCTs are needed to confirm the demonstrated benefits of healthy dietary patterns for the treatment and prevention of anxiety.

Macronutrients and anxiety.

There has been limited investigation of how macronutrient consumption relates to anxiety in clinical trials or observational analyses. However, several studies have examined the effect of n-3 fatty acids on anxiety; this will be the focus of the following sections.

Clinical trial evidence for the effect of macronutrient composition on anxiety.

In a recent review, authors concluded there is no clinical trial evidence for benefits of n-3 fatty acids on anxiety disorders in patients who are taking medications for anxiety disorders.[105] However, there is some evidence from small clinical studies showing benefits of n-3 fatty acids for anxiety. In a study of undergraduate students who experienced significant anxiety associated with test taking, a mixture of n-3 and n-6 fatty acids (2 capsules daily that provided a total of 90 mg of α-linolenic acid and 360 mg of linoleic acid) improved measures of appetite, mood, concentration, fatigue, and organization.[106] In a study of 22 individuals with substance use disorder, supplementation with 2250 mg/d EPA plus 500 mg/d DHA for 3 months significantly decreased anger and anxiety scores.[107] Similarly, in a Polish study of 52 survivors of a heart attack, 1 month of supplementation with 465 mg/d EPA plus 375 mg/d DHA (in addition to pharmacotherapy) decreased anxiety by approximately 10%; depressive symptoms also decreased (≈ 22%).[108]

With respect to seafood, there is evidence that long-chain n-3 fatty acids EPA and DHA from Atlantic salmon decrease anxiety.[109] In a RCT of men (n = 95), consumption of salmon (150 to 300 g/serving 3 times per week) reduced emotional activation and cognitive worry by approximately 10%, compared with a control group (who ate chicken, pork, or beef 3 times per week), after 23 weeks. Fatty fish are not only a source of n-3 fatty acids but also other nutrients, including vitamin D, iodine, selenium, and protein, which may contribute to the results observed.

Epidemiological evidence relating macronutrient composition to anxiety.

Observational evidence suggests higher intake of oily fish and long-chain n-3 fatty acids is associated with reduced risk of anxiety. In the Seguimiento Universidad de Navarra Prospective Cohort Study conducted in Spain,[110] oily fish consumption was associated with decreased risk of a composite of mental disorders, including depression, anxiety, and/or stress. In this study, participants with moderate consumption of fish (83–

112 g/d) had a 30% reduced risk for a composite of mental disorders. In addition, lower intakes of fish were associated with greater anxiety and higher intakes were associated with lower anxiety. In a study conducted in Australia,[111] consumption of the n-3 fatty acid DHA was linearly related to a decrease in anxiety disorders. Individuals in the highest tertile of DHA intake had an approximate 50% reduction in risk of anxiety disorders. Reduced anxiety has also been observed with higher n-3 consumption in pregnancy. In the Avon Longitudinal Study of Parents and Children study conducted in the United Kingdom, consumption of more than 1.5 g/wk of long-chain n-3 fatty acids from seafood (~6 servings per week of seafood from fatty fish) was associated with a decreased risk of anxiety in pregnant women.[112] Women with no n-3 PUFA intake from seafood had a 2-fold increased risk of anxiety symptoms. In another study of pregnant women in Singapore, lower plasma n-3 PUFA concentrations (a marker of intake) were associated with increased anxiety before the birth of their babies.[113]

Micronutrients and anxiety.

Findings from preclinical and clinical studies show magnesium and zinc deficiency can lead to anxiety, and supplementation can help alleviate anxiety-like symptoms.[114] Magnesium intake along with other combination therapies was effective in treating anxiety and related disorders in 3 clinical trials.[115–117] One study found the combination of magnesium (200 mg/d) and vitamin B_6 (50 mg/d) had a small synergistic effect and reduced anxiety-related symptoms.[116] Another study showed that magnesium taurinate or glycinate (125–300 mg at each meal and bedtime) alleviated anxiety-like symptoms in patients with magnesium deficiency.[118] There is some evidence for an anxiety benefit of vitamin C supplements in a healthy young population[119] as well as in individuals with type 2 diabetes.[120] One study found that 500 mg daily of vitamin C for 14 days significantly reduced anxiety levels.[119] The effects of vitamin C and E supplements on anxiety, depression, and stress were evaluated in patients with type 2 diabetes, and vitamin E significantly decreased anxiety.[120] Interestingly, there is some evidence that multivitamin and mineral supplementation in children[121] and adults[112,122,123] reduces anxiety. Also, vitamin D serum levels were lower in men and women with anxiety disorders (and depression); however, the effect of vitamin D supplementation on anxiety is not known.[124]

There is some evidence that amino acids L-lysine and L-arginine, both of which may influence neurotransmitters involved in stress and anxiety, may be beneficial.[125] When individuals consuming a lysine-inadequate diet consumed a lysine-fortified wheat, there were significant improvements in chronic anxiety and cortisol levels.[126] In another trial of healthy men with high levels of perceived anxiety, supplementation with a mixture of L-lysine and L-arginine (3 g of each per day) normalized stress-induced hormone responses.[127] Similarly, another study found that daily supplementation with L-lysine and L-arginine (2.64 g of each per day) reduced both state and trait anxiety similarly in men and women.[128] Thus, a combination of L-lysine and L-arginine may be a potentially useful intervention in individuals with high levels of mental stress and anxiety.

Summary recommendations on diet and anxiety

The collective scientific evidence for foods, nutrients, and anxiety suggests there are benefits of marine-derived n-3 fatty acids, as well as fatty fish. With respect to micronutrients, there is some evidence that magnesium, zinc, some vitamins (ie, B vitamins, vitamin C, and vitamin E), the amino acids lysine and arginine, and a multivitamin and mineral supplement may be helpful in the prevention and treatment of anxiety disorders. Thus, a healthy dietary pattern that meets food-based and nutrient recommendations may help reduce anxiety. A healthy dietary pattern will provide the micronutrients magnesium, zinc, and some vitamins (ie, B vitamins, vitamin C, and vitamin E), and n-3 fatty acids that favorably affect anxiety.

CONCLUSION

An approach that integrates knowledge about dietary patterns, specific foods, and biological mechanisms of action of critical nutrients is needed to develop evidence-based clinical practice guidelines[129–131] to decrease the risk of depressive illnesses and improve their clinical management. A growing evidence base suggests that diet and nutrition have a causal role in behavioral health disorders, and dietary interventions may improve outcomes in individuals with these disorders. Accordingly, nutritional medicine should be a focal point in psychiatric practice for behavioral health disorders, including risk for suicide, psychotic disorders, and other conditions not reviewed here. Major limitations of research in this area include the difficulty in establishing an evidence base, because of the complex, multidimensional nature of behavioral health disorders, reverse causation, residual confounding, and lack of objective biomarkers. Nevertheless, current evidence suggests a nutritionally adequate, healthy dietary pattern is rich in fruits, vegetables, whole grains, low-fat dairy, and lean protein foods. In addition, fatty fish high in n-

3 fatty acids, and olive oil have benefits. The 3 food-based Healthy Eating Patterns that are recommended in the 2015–2020 Dietary Guidelines for Americans (Healthy US Style Eating Pattern, Healthy Mediterranean-Style Eating Pattern, Health Vegetarian/Vegan Eating Pattern) are examples of healthy dietary patterns that could be implemented to improve behavioral health. Vegetarian and vegan diets should ensure nutrient adequacy, especially sufficient intakes of n-3 fatty acids (eg, algae, walnuts, flax), iron (eg, legumes, green leafy vegetables), and vitamin B_{12} (via fortified foods or supplements). Additional research is needed to increase understanding of how diet- and nutrition-related biological mechanisms affect behavioral health disorders for the evolution of better nutrition-based interventions to reduce the impact (both health and economic) of these disorders on individuals, families, and society.

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