REVIEW

The Role of the Gut Microbiota in Dietary Interventions for Depression and Anxiety

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ABSTRACT

There is emerging evidence that an unhealthy dietary pattern may increase the risk of developing depression or anxiety, whereas a healthy dietary pattern may decrease it. This nascent research suggests that dietary interventions could help prevent, or be an alternative or adjunct therapy for, depression and anxiety. The relation, however, is complex, affected by many confounding variables, and is also likely to be bidirectional, with dietary choices being affected by stress and depression. This complexity is reflected in the data, with sometimes conflicting results among studies. As the research evolves, all characteristics of the relation need to be considered to ensure that we obtain a full understanding, which can potentially be translated into clinical practice. A parallel and fast-growing body of research shows that the gut microbiota is linked with the brain in a bidirectional relation, commonly termed the microbiome–gut–brain axis. Preclinical evidence suggests that this axis plays a key role in the regulation of brain function and behavior. In this review we discuss possible reasons for the conflicting results in diet–mood research, and present examples of areas of the diet–mood relation in which the gut microbiota is likely to be involved, potentially explaining some of the conflicting results from diet and depression studies. We argue that because diet is one of the most significant factors that affects human gut microbiota structure and function, nutritional intervention studies need to consider the gut microbiota as an essential piece of the puzzle. *Adv Nutr* 2020;11:890–907.

Keywords: microbiome–gut–brain axis, depression, anxiety, mood, mental health, nutritional psychiatry, microbiota, diet, nutrition

Introduction

Around 15–20% of people will experience mental health disorders such as a depressive episode or anxiety disorder in their lifetime (1, 2), and anxiety and depression are ranked in the top 10 causes of the global burden of disease (3, 4). Unfortunately, our understanding of these disorders and ability to effectively treat them are poor; for example ∼30%–40% of those with depression do not adequately respond to pharmacological or psychological treatment (5). The high impact on individual quality of life, as well as on the public health system, means that preventing and treating anxiety and depression is a global priority. Consequently, there has been a call for a broader research approach with more interdisciplinary efforts (6, 7). Recent approaches in depression and anxiety research are investigating *1*) the links between diet and mood, and *2*) the influence of gut microbiota on neurobiology and behavior, termed the microbiome–gut–brain axis (MGBA). There is emerging evidence showing a strong influence of both diet and gut microbiota on emotional behavior and neurological processes, and because the gut microbiota is strongly affected by diet (8), these 2 factors are also intertwined (**Figure 1**). With increasing understanding of the mechanisms involved in the complex interplay between diet and the gut microbiome and its impact on anxiety/depression, specific dietary patterns that can help prevent anxiety and mood disorders can be identified. In addition, the use of dietary intervention may prove to be an attractive and cost-effective alternative or adjuvant therapy to clinically treat these disorders. This review discusses the reasons for conflicting research on the link between diet and depression, and how any diet and depression relation is likely to be influenced by changes in the MGBA. The focus of the review is on whole diets and, and although interactions of the gut microbiota with individual components of the diet are discussed, separate dietary supplements (such as probiotics) are not included in detail.

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Abbreviations used: AA, arachidonic acid; FA, fatty acid; FFAR, free fatty acid receptor; FODMAP, Fermentable Oligosaccharides, Disaccharides, Monosaccharides, And Polyols; FOS, fructooligosaccharide; GABA, γ-aminobutyric acid; GF, germ-free; GOS, galactooligosaccharide; HFD, high-fat diet; HPA, hypothalamic–pituitary–adrenal; MGBA, microbiome–gut–brain axis; PDX, polydextrose; SPF, specific pathogen–free.

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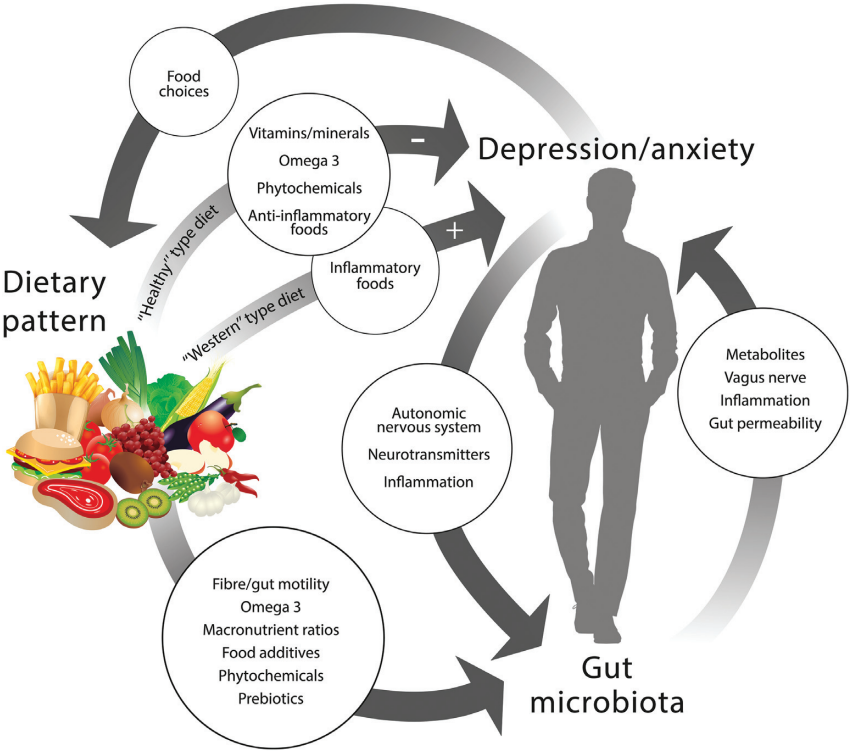

FIGURE 1 Diet has been linked with the risk of developing depression and anxiety; there are direct effects from dietary components which could mediate this relation. Emerging research suggests that the gut microbiota is also associated with depression and anxiety in a bidirectional relation. Because diet also has a large influence on gut microbiota, the gut microbiota should be considered a key variable in the diet–depression relation.

Current Status of Knowledge

The relation between diet and depression

Research shows that there is a relation between diet and depression; however, there are conflicting results from studies and the directionality and mechanism of the relation are currently unclear. Many correlative studies in healthy adults show that a lower incidence of depression occurs in those who eat according to "healthy" dietary patterns, characterized by an abundance of vegetables, fruits, cereals, nuts, seeds, and pulses, as well as moderate amounts of dairy, eggs, and fish and unsaturated fats (9), including the Mediterranean diet (10, 11), Japanese diet (12, 13), and Norwegian diet (14). In contrast, a "Western" dietary pattern, consisting of sweet and fatty foods, refined grains, fried and processed foods, red meat, high-fat dairy products, and low fruit and vegetable intake, is associated with higher depression incidence (10, 15, 16). However, not all studies show an association, with many finding no association (17–20) or showing an effect only from a specific food [e.g., tomatoes (18)].

Conflicting results from studies are potentially due to many factors. There is possible recall bias due to the use of FFQs, and difficulty in controlling for all confounding variables (21). The recall bias has not been addressed and may be a specific problem for assessing diet and depression, because depression can affect memory (22). Participant and researcher expectation bias is another issue in randomized controlled trials. Because the variables being measured rely on participant reporting, blinding is important to prevent expectation bias. However, blinding of the participants to the hypothesis is difficult. Dieticians/nutritionists and psychologists who deliver the separate arms of the trial should also be blinded as to the study hypothesis, but in practice this is rarely done.

Reverse causality is possible. Stress and depression can also alter taste thresholds (23), perception of sugary and fatty foods (24, 25), and food choices (26–28). A 10-y longitudinal study in France showed an association between depression incidence and poor diet, but found that there was probably reverse causality, with depression increasing the risk of poor eating behaviors (29). A reanalysis of a longitudinal study in Australia showed that those with an existing depressive episode had a poorer diet, but not those with only historical depression (30). The authors suggest that this could be due to reverse causality, but alternatively could be due to altered dietary habits after depression treatment in order to prevent depression recurrence, an interpretation that is supported by a study showing that 20% of people with depression intentionally improve their diet (31).

Attempts to determine the direction of causality from prospective studies and randomized controlled trials have

shown similar mixed results. A meta-analysis of prospective studies identified that a high-quality diet, regardless of its type, as well as increased fish and vegetable intake, was associated with a lower incidence of depression, with a dose–type relation with compliance to the healthy diet. In contrast, however, this meta-analysis showed that a low-quality diet was not found to be associated with an increased risk of depression, and the results showed a high level of heterogeneity between studies (32).

A systematic review of randomized controlled trials by Opie et al. (33) found that study design varied in terms of delivery method, type of intervention, and the study population. Few studies have been done in medically healthy people, and over half of the studies showed no effect from the intervention. Interventions that were successful in improving depressive symptoms had a single delivery mode (e.g., face to face), had been delivered by a qualified nutritionist or dietitian, and were more likely to recommend an increase in vegetables as opposed to a cholesterol-lowering diet or a reduction in red meat.

The mixed results and difficulties in research design do not mean that there is not a clinically meaningful relation. There are plausible mechanisms for how diet can affect depression, and bidirectionality is probable. Depression is primarily a psychological illness and the strength and importance of a diet–depression relation will vary depending on individual psychological traits, including personality, thought patterns, and coping skills. Psychological variables are not usually adequately controlled or accounted for in nutrition studies. The finding that the diet–depression relation is stronger with a healthy diet than with an unhealthy diet could be due to people less susceptible to depression being more resilient to the effects of an unhealthy diet, and potentially diluting any measured effect. In addition, there are likely to be geographical differences in the strength of the relation, as variations in micronutrient content in soils, and consequently in foods, occur [e.g., low selenium content in New Zealand soils (34)]. Prospective studies often attempt to determine the direction of causality by excluding those who already have depression from the analysis, and then examining the rates of depression developed in the rest of the cohort against the different dietary patterns. The problem with this approach is that not everyone has an equal risk of developing depression, because there are strong genetic, epigenetic, and environmental components to being vulnerable to depression (35). By excluding those who already have depression, the sample is biased towards those who are less vulnerable to developing depression, and for whom any link between diet and depression is likely to be much weaker. In addition, Molendijk et al. (32) suggested that controlling for baseline depression severity could cancel out diet–depression effects because the influence of poor diet on depressive symptoms may have begun years earlier. It is also possible that poor diet increases vulnerability to developing depression under stress, rather than directly causing depression, and therefore a study undertaken in a cohort with low environmental stress may not reach the tipping point in numbers developing depression needed to reveal the relation if it exists.

Physiologically, there are multiple plausible mechanisms by which diet can directly influence symptoms of anxiety and depression. The etiology of depression itself is not fully established but many biological and neurological changes are linked to depressive symptoms. A reduction in monoamine neurotransmitters, especially serotonin, is the most well-known mechanism and the pharmacological target of most antidepressant drugs (36). But monoamine deficiency is most likely only a cause of depressive symptoms in a vulnerable population (37). Other mechanisms found to be linked to depression include a dysfunctional hypothalamic–pituitary–adrenal (HPA) axis (38); immune-inflammatory, oxidative, and nitrosative pathways (39–42, 30, 43–48); neuroinflammation (including activated microglial cells) (43); altered vagus nerve tone (49); neurotrophic changes, including structural changes such as decreased hippocampus volume (50, 51) and region-specific changes in brain-derived neurotrophic factor concentrations (52); an imbalance between neural excitation and inhibitory signaling (53–55); and alterations in tryptophan metabolism, including the kynurenine pathway (56).

A number of micronutrients have been found to be low in those with depression or an increased risk of depression, including zinc, magnesium, selenium, iron, and vitamins D, B-12, B-6, E, and folate (57–62). These micronutrients may affect depression risk via effects on the production and activity of monoamine neurotransmitters such as serotonin (63–68), alterations to the HPA system (62), glutamatergic signaling (62), or inflammatory and oxidative stress (62, 69). A diet high in fruits and vegetables has higher amounts of these micronutrients. Plants also contain effective antioxidant phytochemicals, such as vitamin C, polyphenols, and flavonoids, which have been shown to have antidepressant-like or anxiolytic effects (70–73). SFAs, and PUFAs such as DHA (22:6n–3), EPA (20:5n–3), and arachidonic acid (AA; 20:4n–6), are incorporated into neural tissue and are important for its function (74). The ratio of the different fatty acids (FAs) affects function; for example, increased SFA decreases cell membrane fluidity and permeability (75), and a low ratio of DHA to AA may increase systemic and brain inflammation (76, 77). Healthy-style diets, especially the Mediterranean diet, are anti-inflammatory (78) and may lower the risk of depression by reducing inflammation.

An understudied aspect in the diet–depression relation which could explain some of the inconsistencies is the diet–microbiota–mood relation. Emerging evidence shows that the gut microbiota is linked to emotional behaviors thought to represent symptoms of both depression and anxiety, and because the gut microbiota is highly influenced by diet, diet can influence this relation.

The link between the gut microbiota, depression, and anxiety

Research into the MGBA began with the observation that there is a high comorbidity of anxiety and depression in those

with inflammatory bowel disease (79, 80) and irritable bowel syndrome (79–82). In addition, gut microbiota composition in individuals with anxiety or depression (including those in remission) differs from that in healthy controls (83–85), and animal models of depression show altered gut microbiota compared with controls (46).

Early studies in mice showed that gut infections or chemically induced colitis caused an increase in patterns of behavior thought to represent anxiety, including decreased exploration (86) and increased behavioral inhibition (87, 88). The direct effect of gut microbiota on emotional behaviors was shown in studies which identified that anxiety-like behaviors differ between germ-free (GF) rats and mice (born and raised in a microbiota-free environment) and animals with normal, specific pathogen–free (SPF) gut microbiota (89–92). Colonization of GF animals with SPF gut microbiota has been shown to ameliorate the behavioral differences (90, 92, 93). Fecal transplants from anxious-type mice into a more resilient strain increase anxiety-like behaviors in the resilient strain, and vice versa (94). Probiotic supplementation has also shown promise, with a reduction in anxiety and depression reported in many human and animal studies (95–99). Probiotics seem to also be protective against the development of anxiety due to gut infection (88) and immunodeficiency (100).

Although there is convincing evidence that microbiota can be linked to emotional behaviors, we do not fully understand the mechanisms, nor the clinical relevance. Studies in humans are still few, and often do not translate from animal studies, possibly because they often use healthy people without depressive symptoms (101). Inconsistencies in behavioral changes in animal studies often occur between stress-sensitive and stress-resilient rodent strains (89–92) and between males and females (90, 91), suggesting that the host–microbiota relation may depend on host genotype. There may be critical windows of development during which the gut microbiota have more effect: for example, early life (93), adolescence (90, 102, 103), or during gestation (104–106).

Microbial-mediated mechanisms of mood and neurological processes are still being elucidated (88). At the systemic level, immune modulation has been found in GF mice (90), antibiotic-treated mice (103), and with probiotic supplementation (88, 90, 98, 99, 103, 107–111). Some studies have shown no evidence of inflammation alongside behavioral changes (88, 108) or only a partial effect (98, 109, 110); however, even subclinical gut infection without overt inflammation caused behavioral changes in mice (87). Increased HPA axis activation (96, 102) and alterations to the tryptophan/kynurenine metabolism have also been found (88, 90, 107, 112–115). In the gut, changes have been found for SCFAs (113), gut motility (100), and gut permeability (110, 116–118). The vagus nerve may be required (97, 102, 119–121), but not always (88, 94). It is likely that multiple parallel mechanisms are at play, and the mechanisms of the effect of the gut microbiota are specific even to the species level.

Microbial metabolites may play a role, with some bacteria able to produce the same neuromodulating substances that are found in the nervous system of animals, including γ-aminobutyric acid (GABA), acetylcholine, dopamine, serotonin, and norepinephrine (122–126). GABA, acetylcholine, and noradrenaline are also all immunomodulatory (127, 128). SCFAs, particularly butyrate, contribute to decreased gut inflammation (129) and enhanced gut epithelial integrity (130). They stimulate the secretion of serotonin from enterochromaffin cells in the gut (115, 131, 132), which mainly affects gut motility but can also activate the vagus nerve, and enter the circulation (132). SCFAs activate free fatty acid receptors (FFARs), which seem to have a direct anti-inflammatory effect on microglial activation (133), as well as being generally anti-inflammatory, because FFARs are present on neutrophils and dendritic cells (134). No difference in SCFAs was found in the fecal samples of people with depression compared with healthy controls, but when the fecal samples were transplanted into mice, an increase in fecal acetate and total SCFAs was found (113). Gut bacteria are also a significant source of vitamins, including vitamin K-2 (menaquinone) and the B-vitamins niacin (B-3), biotin (B-7), folate (B-9), and pyroxidine (B-6) (135–139). Biotin and niacin are immunomodulatory, and deficiency could contribute to gut and systemic inflammation (129, 140). Serum folate is lower in those with depression (141) and may be associated with symptom severity (61) and responsiveness to antidepressant treatment (142). Pyroxidine is an essential cofactor in many enzymes in the kynurenine pathway, which is altered in those with depression (55). GF rats show an increased susceptibility to pyroxidine deficiency (137).

Changes in gut microbiota with depression and anxiety

The MGBA findings of behavioral effects with probiotic or inflammatory bacteria broadly fit with the microbial profiles associated with positive or negative mental health, although there is no specific gut microbiota composition profile linked to anxiety or depression. Comparisons of microbial changes in humans with depression show a variety of changes compared with healthy controls, but show a general pattern of increases in potentially harmful and inflammatory bacteria such as *Proteobacteria*, which are normally minor in relative abundance, alongside a decrease in commensal bacteria, which are normally more abundant (83, 84, 113, 143–145). In those with Generalized Anxiety Disorder, fewer changes were found but a similar reduction in commensal bacteria was seen (85). The lack of an identified depression or anxiety "gut microbiota profile" is likely to be due to variation in the methods used to evaluate gut microbiota composition and gene abundance, and individual variation in the human gut microbiota (146). Although there are still many unknowns relating to the MGBA and its mechanisms, the emerging evidence, combined with the effect of diet on microbiota, supports its important role in the diet–mood relation.

Interactions of Diet with the MGBA

Whole diet

There is a paucity of research measuring the effects of whole diet on microbiota as well as depressive symptoms, and studies on diet and anxiety in humans are still needed. However, dietary patterns associated with a risk of depression are in line with changes in microbial composition and functions, which MGBA research shows can affect emotional behavior in rodents. Adherence to the Mediterranean diet reduces the numbers of inflammatory/pathogenic bacteria such as *Escherichia coli*, and increases key commensal bacteria such as *Bifidobacteria* (147), *Clostridium cluster XVIa*, and *Faecalibacterium prausnitzii* (148). It also increases microbial metabolites including fecal SCFA concentrations (149), phenolic metabolites, benzoic acid, and 3-hydroxyphenylacetic acid (148). Vegetarian or entirely plant-based diets have been shown to alter microbial composition (150–152) and reduce gut inflammation (150). A dietary pattern defined by fast-food consumption reduced *Lactobacilli* (149). A high-fat/low-carbohydrate diet, regardless of the type of fat, decreases total bacteria (153).

Many of the individual dietary elements that are associated with an increased or decreased risk of developing depression also alter the gut microbiota (refer to **Table 1**). It is plausible that the effect of a dietary component on the gut microbiota may partially or wholly mediate the effect of that dietary component on mood.

Fish and omega-3 FA intake

Although "healthy" dietary patterns containing fish are found to be associated with a lower risk of depression (10, 15, 29, 154–157), other studies show fish to be 1 component of dietary patterns that increase the odds of depression (13) or are inflammatory (158). When looked at in isolation, there is evidence for a decreased risk of depression (159), increased risk (160–162), or no relation (163–166). Randomized controlled trials comparing fish oil with olive oil found no difference in mood improvement (167, 168); however, neither group was initially deficient in ω-3 FAs. Meta-analyses have found that ω-3 FA dietary supplementation (from fish oil or added fish) has a positive effect on mood in those with symptoms of depression, but not in healthy controls (169, 170). There may be an optimal dose, because some studies have shown a nonlinear association between ω-3 FA and depressive symptoms, with the highest doses being less effective than moderate doses (162, 165). People with depression have lower concentrations of ω-3 FAs in their RBC membranes (171–173), possibly through oxidative damage (172) rather than lower ω-3 FA intake. This observation supports emerging evidence that those with depression have higher levels of inflammation and oxidative stress (174, 175).

Lower intake of fish or ω-3 FA may affect depression risk via microbiota-induced inflammation. Research in mice suggests that the anti-inflammatory effect of ω-3 FA may be due to its effect on microbiota (176). A diet comprising a high ratio of ω-6 FA to ω-3 FA (~25:1), as is typical of a Western-style human diet, fed to wild-type mice caused elevated serum concentrations of the metabolic endotoxemia markers LPS and LPS-binding protein, as well as increased gut permeability compared with that in *fat-1* transgenic mice fed the same diet. The *fat-1* mice can endogenously produce ω-3 FA from ω-6 FA and therefore had a lower gut ratio of 4:1. The difference in serum LPS (but not the cytokine IL-1β and serum triglycerides) was eliminated when the mice were given antibiotics, or when ω-3 FA dietary intake was increased. The mechanism was found to be an ω-3 FA-dependent increase in production of an endogenous antimicrobial peptide, gut alkaline phosphatase, which suppresses proendotoxic bacteria.

Another study in rats showed that supplementation of the ω-3 FAs EPA and DHA was associated with restoration of disturbed gut microbiota caused by early-life stress (maternal separation) (177). In a follow-up study, pregnant mice and then their offspring were given diets that were either ω-3 FA deficient or ω-3 FA supplemented (178). The ω-3 FA–deficient diet caused increased fear-induced freezing behavior, decreased sociability, and increased depressive behavior in the offspring when they had become adults. The diets were, not surprisingly, associated with differences in FA composition in the brain, but also differences in fecal microbiota profiles. The changes in microbiota numbers showed the ratio of *Firmicutes* to *Bacteroidetes* was increased by ω-3 FA deficiency. In the ω-3 FA–supplemented group, *Bifidobacterium* and *Lactobacillus* were present in higher numbers in adult mice, the ratio of *Bifidobacterium* to *Enterobacteria* was higher, and *Anaeroplasma*, *Clostridium*, and *Peptostreptococcaceae* numbers were lower, in both adolescents and adults.

Fish and ω-3 FAs may play additional roles to those previously assumed in the link with depression. Rather than there being only a straightforward relation between EPA or DPA concentrations and neural processes, dietary intake of ω-3 FA may also (or only) be important for those with gut dysbiosis–induced systemic inflammation, and the ratio of ω-3 FA to ω-6 FA in the diet may also be critical.

Micronutrient intake

Microorganisms require many of the same micronutrients that humans do, and obtain many of these micronutrients through the host diet. Subsequently, host micronutrient intake can affect the gut microbiota composition and function. Altered gut microbiota has been found in mice with a magnesium-deficient diet and was associated with increased depressive-like behavior (179). Whether the change in behavior was caused by or simply additional to a change in gut microbiota is unclear. Vitamin D intake also affects the gut microbiota; supplementation altered the gut microbiota in stool samples in patients with Crohn disease but not healthy controls (180), or caused a change in healthy adults but only in the stomach and duodenum (181). In infants, the vitamin D status of their mother during pregnancy influenced their gut microbiota at 1 mo old, but a supplement given directly to the infant did not, possibly due to different baseline concentrations of serum vitamin D in the infants (182). The different gut regions (stool sample compared with

TABLE 1 Examples of published literature evidence (from in vitro, animal, and human studies) of components within dietary patterns related to depression in humans or emotional behaviors in animals, which directly affect the host but also interact with the gut microbiota[1]

Dietary component	Effect	Summary	Subject	Ref.
Phytochemicals				
Cocoa polyphenols	Affected mood	In an RCT in adults, 500 mg supplement for 30 d increased self-rated calmness and contentedness compared with placebo.	Human	Pase et al. (183)
	Altered microbial growth	A 6-wk diet with 10% cocoa in rats caused a decrease in *Bacteroides*, *Clostridium*, and *Staphylococcus* genera in feces.	Animal	Massot-Cladera et al. (184)
		In vitro digestion with 1 g cocoa powder/60 mL water. 38.6% of phenols were solubilized, and an increase in *Bifidobacteria*, *Lactobacilli*, and butyrate was found.	In vitro	Fogliano et al. (185)
	Altered immune function	A 6-wk diet with 10% cocoa in rats caused an altered toll-like receptor pattern and increased gastrointestinal immunoglobin A secretion.	Animal	Massot-Cladera et al. (184)
Blueberry extract (anthocyanins)	Affected mood and cognition	In a BCT, in children and young adults, a single drink containing 253 mg anthocyanins increased positive but did not change negative affect scores using the "Positive and Negative Affect Scale" compared with a placebo drink.	Human	Khalid et al. (186)
		A 5% blueberry drink given to rats for 8 wk protected against cognitive impairment during chronic mild stress.	Animal	Guo et al. (187)
	Altered host metabolites	Decreased plasma norepinephrine and dopamine concentrations, and brain concentrations of antioxidant compounds due to 8 wk of chronic mild stress were attenuated by a 5% blueberry drink.	Animal	Guo et al. (187)
Fiber (prebiotic)				
GOS, PDX, and FOS	Attenuated stress-induced behaviors and mood, and gene expression in the brain	Male rats were fed diets containing GOS + PDX for 4 wk and then underwent inescapable stressors. The prebiotic reduced stress-induced exaggerated freezing and deficit in escape latency, and attenuated c-fos mRNA in parts of the brain.	Animal	Mika et al. (188)
		Male and female rats underwent early-life stress (maternal separation model). Prebiotic supplementation of GOS + FOS for 5 wk after the stress attenuated stress-induced deficits in spatial memory and locomotion, but not anxiety-like behaviors.	Animal	McVey Neufeld et al. (189)
		RCT, patients with depression: 8 wk supplementation with 5 g GOS resulted in decreases in scores on the Beck Depression Inventory compared with placebo.	Human	Kazemi et al. (190)
		Healthy volunteers given either FOS or GOS daily for 3 wk. Salivary cortisol awakening response and emotional bias (attention to negative information) were decreased after GOS but not FOS.	Human	Schmidt et al. (191)
	Altered the gut microbiota	Prebiotic diet of GOS + FOS increased *Lactobacillus rhamnosus* and also *Lactobacillus* spp.	Animal	Mika et al. (188)
		44 elderly subjects, given 5.5 g/d GOS or placebo for 10 wk in a double-blind, placebo-controlled, crossover study. Increase in *Bifidobacterium* spp., *Lactobacillus Enterococcus* spp., *Clostridium coccoides–Eubacterium rectale*, and a decrease in *Bacteroides* spp., *Clostridium histolyticum* group, *Escherichia coli*, and *Desulfovibrio* spp.	Human	Vulevic et al. (192)
	Altered immune function	Increases in immune function, including reduced proinflammatory cytokines and increased anti-inflammatory cytokines, phagocytosis, and NK cell activity.	Human	Vulevic et al. (192)
Wheat arabinoxylan	May counteract effects of high-protein diet on the gut microbiota	In pigs fed a 4-wk Western-type diet, added soluble fiber (wheat arabinoxylan) increased carbohydrate fermentation and reduced protein fermentation and fermentation products such as ammonia.	Animal	Williams et al. (193)

(*Continued*)

TABLE 1 (*Continued*)

Dietary component	Effect	Summary	Subject	Ref.
Vitamins/minerals				
Vitamin D	Regulated gut physiological processes	Vitamin D receptors in the gut regulate processes including epithelial barrier function and immune processes.	Review	Barbáchano et al. (194)
	Associated with changes in the gut microbiota	Plasma 25-hydroxyvitamin D and vitamin D supplementation in women in their 36th week of pregnancy were measured, and compared with fecal samples in their 1-mo-old infants. Increased concentrations of both were associated with decreased *Bifidobacterium* spp. and *Clostridium difficile* and increased *B. fragilis*.	Human	Talsness et al. (182)
Magnesium	Dietary deficiency altered behavior	30 mice fed a magnesium-restricted diet for 6 wk had increased immobility in the forced swim test and increased hippocampal IL-6 compared with mice fed a normal diet.	Animal	Winther et al. (179)
	Associated with changes in the gut microbiota	The cecal gut microbiota was also altered, with cluster analysis showing significant differences between the diets.		
Vitamin A	Associated with changes in the gut microbiota and the gut mucosal barrier	A vitamin A–deficient diet in rats increased total bacteria, decreased *Lactobacillus* spp., and increased *Escherichia coli*. Mucin-producing goblet cells were altered and expression of toll-like receptors was increased.	Animal	Amit-Romach et al. (195)
		Vitamin A deficiency in children aged 1–12 mo with persistent diarrhea showed significantly different gut microbiota than in those with normal serum vitamin A concentrations.	Human	Lv et al. (196)
Macronutrients				
ω-3 fatty acids	Immunomodulatory	The metabolic and inflammatory effects in wild-type mice fed a diet with a high ratio of ω-6 to ω-3 were able to be prevented with antibiotic treatment, or by cohousing mice with *Fat-1* transgenic mice, which endogenously produce ω-3 fatty acids.	Animal	Kaliannan et al. (176)
	Increased endogenous antimicrobial defenses	*Fat-1* mice were found to produce increased intestinal alkaline phosphatase, an endogenous antimicrobial compound, which reduced gut permeability and LPS production.	Animal	Kaliannan et al. (176)
	Restored gut dysbiosis	*Fat-1* transgenic mice were found to be protected against gut dysbiosis and obesity caused by a Western-style diet after early-life antibiotic exposure.	Animal	Kaliannan et al. (197)
		Supplementation of 100–250 mg/d ω-3 FA (80% EPA, 20% DHA) for 12 wk to female rats reversed stress-induced gut dysbiosis.	Animal	Pusceddu et al. (177)
	Increased gut microbial metabolites (SCFAs)	An 8-wk open label trial using an EPA/DHA supplement drink or capsule in adult males and females reversibly increased SCFA-producing bacteria including *Bifidobacterium*, *Roseburia*, and *Lactobacillus*.	Human	Watson et al. (198)
	Deficiency affected mood as well as the gut microbiota	An ω-3 FA–deficient diet in pregnant mice and their male offspring resulted in an elevated ratio of *Firmicutes* to *Bacteroidetes* in the offspring, along with altered behavior and immune function.	Animal	Robertson et al. (178)
		Increased depressive behavior (immobility in forced swim test), decreased sociability (three chamber test), isolation-induced ultrasonic vocalizations in adulthood, and decreased memory (novel object recognition test) in both adolescence and adulthood. Increased contextual fear conditioning.		

(*Continued*)

TABLE 1 (*Continued*)

Dietary component	Effect	Summary	Subject	Ref.
High fat, particularly saturated fat	Altered microbiota composition	A high-fat diet in mice decreased *Ruminococcaceae* and increased *Rikenellaceae* compared with a carbohydrate diet.	Animal	Daniel et al. (199)
		Increase in *Firmicutes*, particularly the family *Erysipelotrichaceae*, and decrease in *Bacteroidetes* in mice fed a high-fat diet.	Animal	Fleissner et al. (200)
		Mice fed a low-fat diet who switched to a high-fat diet had a significant shift in microbiome composition within 1 d. Increased *Firmicutes*, particularly the *Erysipelotrichi* class, *Bacilli*, and decreased *Bacteroidetes*.	Animal	Turnbaugh et al. (201)
		BALB/c mice fed a high-fat diet showed alterations in the gut microbiota including an increase in *Firmicutes*, particularly in the families Rumunococcaceae and *Lachnospiraceae*, a decrease in the *Bacteroidetes* phylum, and a resulting decrease in the ratio of *Bacteroidetes* to *Firmicutes*.	Animal	Pyndt Jørgensen et al. (202)
	Altered anxiety-like behavior	Mice fed a high-fat diet displayed less burrowing (anxiety-like) behavior, and displayed reduced memory in the Morris water maze test compared with mice fed a control diet. The diets were not isocaloric, and the high-fat diet mice also gained more weight.	Animal	Pyndt Jørgensen et al. (202)
High-fat, high-sugar diet	Altered microbiota composition	A Western-style diet in humanized mice resulted in increased *Erysipelotrichi* class (mainly *Clostridium innocuum*, *Eubacterium dolichum*, and *Catenibacterium mitsuokai* genera) and *Bacilli* class (mainly *Enterococcus* spp. genera). The microbial shift occurred after only a single day.	Animal	Turnbaugh et al. (201)
High-sugar diet	Positive change in behavior when the gut microbiota was not altered	A high-sucrose diet did not alter the gut microbiota in BALB/c mice compared with a control diet and did alter some behaviors, but in a positive direction (increased latency to immobility in the forced swim test, less goal-orientated burrowing, and less anxiety-like behavior in the triple test).	Animal	Pyndt Jørgensen et al. (202)
Red meat	Modified gut microbiota composition	A comparison between a diet rich in red meat or whole grains (10-wk crossover trial) showed that increased red meat consumption increased the genera *Clostridium* spp. from the phylum *Firmicutes*.	Human	Foerster et al. (203)
	Microbial metabolism of heme-rich meat increases oxidative compounds	Comparison of meat types varying in heme content (beef, pork, chicken) in an in vitro digestion model showed that heme-rich meat caused higher concentrations of the nitrosoxide compound–derived DNA adduct O^6-carboxymethylguanine.	In vitro	Vanden Bussche et al. (204)
Food additives				
Emulsifiers CMC and P80	Altered gut microbiota composition	C57Bl/6J mice were given either CMC or P80 emulsifiers at 1% in their drinking water from weaning until 3 mo old. The gut microbiota was altered by the treatment. Interestingly the outcomes differed between males and females. In males, *Firmicutes* phylum and *Oscillospria*, *Coprococcus*, and *rc4_4* genera were reduced, as well as reduced *Dorea* with P80, and reduced *Bacteroides*, *Burkholderia*, *Clostridium*, and *Veillonella* with CMC. In females, *Bacteroides*, Sphingomonadales, *Sphingomonas*, and *Ruminococcus* were reduced, and there was an increase in *Anaeroplasma* with P80, and the *Proteobacteria* phylum and *Clostridium* and *Burkholderia* genera with CMC.	Animal	Holder et al. (205)
	Altered anxiety-like behavior	Treatment with emulsifiers decreased sociability in the 3-chamber test in females only, and increased locomotion in the Elevated Plus Maze in males only. No difference found in forced swim test or light-dark box.		

[1] BCT, blinded crossover trial; CMC, carboxylmethylcellulose; FOS, fructooligosaccharide; GABA, γ-aminobutyric acid; GOS, galactooligosaccharide; PDX, polydextrose; P80, polysorbate 80; RCT, randomized controlled trial.

upper gastrointestinal tract) may explain the differences in these studies, and also suggest that a healthy gut may respond differently than an inflamed gut. Research into whether modulation of the gut microbiota by magnesium and vitamin D supplementation is via immune modulation, and whether vitamin D affects behavior, is lacking.

Iron is an essential nutrient for many bacteria, and dietary intake of iron affects the gut microbiota composition. Increased colonic iron due to dietary supplementation has been shown to increase gut inflammation and pathogenic bacteria, and a diet deficient in iron has been found to increase the relative abundance of *Lactobacilli* (nonsiderophilic bacteria, which do not require iron) in mice [reviewed in (206)]. Conversely, the relative abundance of many beneficial bacteria, including butyrate producers, was also reduced with an iron-deficient diet in rats, and subsequently SCFA production also decreased (207). Host iron status can influence the ability to fight pathogenic bacteria in the colon, and both high and low iron concentrations are associated with increased pathogen virulence (206). A change in gut microbial composition can also affect iron absorption owing to changes in pH (206). The Western diet contains much more iron than can be absorbed and so the concentration of iron found in feces is high (206). Studies with whole diets should examine how micronutrient intake relates to any changes in the gut microbiota.

Prebiotic foods

A "healthy" dietary pattern contains a larger amount of fruit, vegetables, and wholegrains, which contain prebiotics such as fermentable carbohydrates, polyols, and phytochemicals (208). Prebiotic compounds selectively promote the growth and microbial activity of beneficial bacteria and confer positive health outcomes (208). The higher prebiotic content characteristic of healthy diets may be why the association of depression with diet is stronger for healthy dietary patterns and more variable for poor dietary patterns (9, 32, 157). Prebiotic compounds typically have been shown to increase concentrations of *Bifidobacteria* and *Lactobacillus* but as microbial research techniques have become more sophisticated, we now understand that there are many other beneficial bacteria that are promoted with prebiotics, such as butyrate-producing bacteria. Some dietary fibers are considered prebiotic but not all. Dietary fiber that promotes the growth of all gut bacteria is not considered a prebiotic because numbers of pathogenic bacteria are also increased (208). The most well-researched prebiotics are the soluble fibers "fructans" [fructooligosaccharides (FOSs) and inulin] and galactans [galactooligosaccharides (GOSs)]. Mannanoligosaccharides and xylooligosaccharides are also considered prebiotic. Phenolics and phytochemicals show prebiotic effects, although some of the health benefits may be from microbially produced secondary metabolites. Conjugated linoleic acid (18:2n–6) and PUFAs are also considered candidate prebiotics (208).

Evidence to date for the impact of prebiotics on mood is mixed but mostly positive. Studies in rodents have found reduced baseline and stress-induced anxiety-like and depressive-like behaviors with FOSs and GOSs (individually or mixed) (209), a mixture of GOSs and polydextrose (PDX) (188), and the glycoprotein lactoferrin (188). In both these studies, the mixed supplements had a stronger effect on these behaviors. In rats, GOS and PDX supplementation improved scores in anxiety and memory tests more than a probiotic supplementation (*Lactobacillus rhamnosus* GG), but less than a synbiotic supplement (*Lactobacillus rhamnosus* GG, PDX, and GOSs) (189). In zebrafish, a tendency toward improved behaviors under stress was found with supplementation of mannanoligosaccharides and glucose (β-glucans) (210). A synbiotic (FOS, GOS, and inulin with a probiotic mixture containing *Lactobacillus acidophilus* strain T16, *Bifidobacterium bifidum* strain BIA-6, *Bifidobacterium lactis* strain BIA-6, and *Bifidobacterium longum* strain LAF-5) improved depressive symptoms more than the probiotic only in hemodialysis patients (211). Conversely, increased anxiety-like behaviors occurred in mice after supplementation with resistant starch (212). In a human study, prebiotic supplementation in healthy volunteers improved results in an emotional bias test with GOS, but not FOS (191). Prebiotic supplementation altered the microbiota in all these studies. In those studies in which positive behavioral results were found, increases in *Lactobacillus* species and decreases in the phylum *Proteobacteria* were found (209, 188, 210). Along with increased anxiety-like behavior with resistant starch supplementation, Lyte et al. (212) found an increase in the phylum *Proteobacteria*, but interestingly also an increase in *Bifidobacterium*.

The biological activity of many phytochemicals has been shown to have possible positive health effects, including antidepressant-like or anxiolytic effects (70) and a prebiotic effect (213). The actions of phytochemicals may also be due to secondary metabolites created by microbial utilization (213). Research examining the effect of phytochemicals on both mood and microbiota is lacking.

Macronutrients

A large driver of the effect of diet on the composition of the gut microbiota is variation in macronutrient ratios, amounts, and types. Carbohydrate fermentation tends to increase overall microbial fermentation and SCFA production. The amount of fermentation depends on how much reaches the colon, which is influenced by the amount and type of dietary fiber and prebiotic carbohydrates (214). A plant-rich diet promotes the phylum *Bacteroidetes*, specifically the genera *Prevotella* and *Xylanibacter*, which ferment plant fiber. One study found that a reduction in total carbohydrate in the diet reduced the butyrate-producing *Roseburia/Eubacterium rectale* group. Fermentation of protein generates SCFAs, branched-chain FAs, sulfides, and phenolic and indolic compounds. The sulfides are associated with gut diseases (214). The types of bacteria promoted by protein intake are not well established (214).

Increased dietary fat alters the gut microbiota composition (153, 215, 202, 216–219, 199–201, 220), possibly via the stimulation of bile and its modulation into secondary bile

acid products (153). A high-fat diet (HFD) (72% fat kcal, corn oil and lard) may also affect metabolism, inflammation, and gut permeability via the gut microbiota, likely mediated by LPS and the CD14 receptor. These physiological effects of the HFD were able to be reduced with antibiotic treatment (221). Changes in the gut microbiota with an HFD (45% kcal fat) compared with a control diet (10%–12% kcal fat) in mice include decreases in the beneficial bacteria *Bacteroidetes* (222), *Akkermansia* (223), *Bifidobacteria* (223), and *Lactobacillus* (222, 223) and increases in *Firmicutes*, particularly the potentially inflammatory *Clostridiales* (222, 223), *Enterobacteriaceae* (223), and *Proteobacteria* (222). Counterintuitively, the relative abundances of the families *Ruminococcaceae* and *Lachnospiraceae* (202) and the genus *F. prausnitzii* (153), which are considered beneficial gut bacteria (224), were increased by a 60% kcal HFD.

Some evidence for an effect of macronutrient intake on emotional behavior has been found in rodent studies, mostly with an HFD. Increased anxiety-like behavior has been found in mice fed an HFD comprising 60% kcal unspecified unsaturated FAs (225), 58% kcal hydrogenated coconut oil (226), or 45% kcal lard and soybean oil (227), compared with control diets of ~10% kcal fat. Decreased anxiety-like behaviors have also been found with an HFD (Crisco and corn oil, 90% kcal), compared with a diet high in protein (90% kcal) or carbohydrate (90% kcal), which did not alter these behaviors (228). Another study found no change in anxiety-like behaviors with an HFD (60% kcal), but did find alterations in memory, and also found decreased anxiety-like behaviors with a high-sucrose diet (70% kcal) (202). Support for the role of the gut microbiota as a mediator of any behavioral changes with an HFD comes from a study where a fecal transplant from mice fed an HFD (60% kcal fat) into mice with antibiotic-depleted microbiota (fed a normal diet, 13% kcal fat) increased anxiety-like behaviors (229).

Dietary compounds also interact with each other and may offset their individual effects. Increasing dietary carbohydrate, particularly prebiotic compounds, may reduce some of the protein fermentation products because carbohydrate is a preferred substrate (214). Increased inflammation and endotoxemia in mice caused by an HFD were mitigated by polyphenol supplementation or polyphenol-rich plant extracts (215, 230–233). The polyphenol supplementation was also associated with differences in the gut bacteria, including an increase in *Firmicutes* and *Verrucomicrobia* (231), *Akkermansia* spp. (231, 233), *Faecalibacterium* (233), and *Lachnospiraceae*, specifically *Coprococcus* (215), and a decrease in *Bacteroidetes* (231) or microbial diversity (232). The fat content of these diets varied from 26% kcal (231) and 45% kcal (231) to 60% kcal (232). The fat content in the control diets was low at 0% (231) and 4.1% (232).

Food additives

Western diets include a high proportion of processed foods containing food additives to improve attributes such as shelf life, texture, and palatability. Studies in mice showed that emulsifiers can alter the gut microbiota composition (234, 205), increase the proinflammatory potential of the gut microbiota (234), increase microbiota infiltration of the gut mucosa layer (234), and alter anxiety-like behavior (205). Salt is another food additive that tends to be in high concentration in processed foods and Seck et al. (235) found that high fecal salinity alters gut microbe composition, including a decrease in the beneficial bacteria *Akkermansia muciniphila* and *Bifidobacterium* spp., specifically *B. longum* and *B. adolescentis*. Maltodextrin reduces mucus production and increases gut inflammation by increasing endoplasmic reticulum stress (236). The links between a Western diet and depression may include an effect of food additives on the gut microbiota. Evidence from human studies is needed.

Other considerations

Fermented foods typically contain strains of *Lactobacillus* as well as yeasts, and are likely to be important because they contain both probiotic microbiota and microbial metabolites. Most studies investigating the effect of fermented foods on the gut microbiota or mood have been undertaken using commercially produced yoghurts with very specific microbiota and fall more into the category of supplements than diet, so are not discussed here. However, there is huge scope for research into fermented drinks such as wine and kombucha, or foods such as breads, sauerkraut, kimchi, and yoghurt, and their effect on the gut microbiota and mood.

Individual variation in response to dietary changes needs to be considered. Differences in physiology and baseline microbiota composition may affect how the gut microbiota responds to dietary changes, or to disruption such as during stress or antibiotic treatment. For example, a high (palmitic) fat diet in mice increased *Actinobacteria* and *Firmicutes*, with a decrease in *Bacteroides* and *Proteobacteria*, as well as increasing gut permeability and systemic inflammation in mice that became obese. In contrast, the mice that were resistant to becoming obese with the same diet did not have the same changes in microbiota, or systemic effects (220). Age is a factor that also needs to be taken into account. Dietary changes may be more effective, at least in the short term, in younger subjects. Of a group of urban dwellers who spent 16 d living in a rainforest village and consuming the village diet, the change in gut microbiota composition was greater in the children (237). Because gut microbiota composition and stability change with age, different interventions may be more effective at different life stages or, conversely, disruption to microbiota may have more of an impact at different ages.

Childhood adversity increases susceptibility to developing mood disorders later in life, and episodes of major depressive disorder are commonly preceded by psychosocial stress (238, 239). Stress also alters the gut microbiota (240–244), and the effects of early-life stress on microbiota may extend to adulthood (245). It is therefore plausible that changes in microbiota due to stress at least partly mediate the onset of stress-related depressive or anxious episodes. Dietary intervention during or after stress is a promising area of research (241, 246).

Determining which factors help keep a healthy microbiota composition stable or help correct a dysbiosis may be beneficial. The low–Fermentable Oligosaccharides, Disaccharides, Monosaccharides, And Polyols (FODMAP) diet has a reduced amount of fermentable substrate compared with the amounts in normal diets, and can alleviate gut symptoms such as pain and bloating in those with irritable bowel syndrome, because of reduced gas production by gut microbiota (247). The diet is followed strictly for 2–6 wk until gut symptoms resolve, and foods are then reintroduced to determine individual tolerances. Because of the link between irritable bowel syndrome and depression/anxiety, it is plausible that the low-FODMAP diet could correct a dysbiosis related to altered mood. Initial research findings suggest that for those with irritable bowel syndrome symptoms, a low-FODMAP diet may reduce symptoms of anxiety (248). However, the low-FODMAP diet reduces total bacterial abundance, which may lower the production of bacterial metabolites such as SCFAs that are important in maintaining gut homeostasis. A decrease in *Bifidobacteria* and other beneficial bacteria may also occur (247, 249). The diet is designed as a temporary elimination diet for irritable bowel syndrome and adhering to it long-term is likely to compromise nutritional status. Long-term effects on the microbiota profile are unknown.

There is some evidence that altered gut motility may be associated with mood (250) and that the gut microbiota composition is altered by changes in motility and vice versa (251). Foods that directly affect factors such as gut motility, e.g., those containing soluble or insoluble fiber, may also be able to affect mood by correcting problems with motility, which could be a confounding variable or could be related to changes in the gut microbiota. More research in this area is needed, and it would be useful for food intervention studies to measure changes in gut function concurrently with assessing changes in mood. Other cofactors usually considered in depression research, such as exercise and sleep, also have independent impacts on microbiota (252, 253) and should be considered when assessing relations between foods, mood, and the microbiome.

Conclusions

Research shows that there is a link between diet and depression but conflicting results and limited research mean that we do not yet understand the nature of the relation. There is likely to be a bidirectional relation and it may be of more importance in vulnerable individuals. Because diet is a large influencer of the gut microbiota composition and function, it is likely that changes in the gut microbiota contribute to how diet (whole diet and individual components of diet) may affect depression and anxiety. Limited research in this area is sometimes contradictory and mostly in rodents but does show a pattern of results indicating that the gut microbiota may play a significant role and should be considered in dietary intervention studies. Dietary patterns for positive mental health will likely support the growth of commensal microbiota, decrease the growth of pathogenic and colitis-inducing bacteria, and affect gut barrier permeability and inflammation. In addition, because a change in whole dietary patterns changes the ratio of many dietary components, investigation into these individual components is also important. In dietary studies for depression and anxiety, types and amounts of dietary components (e.g., fat, prebiotics) within the dietary patterns should be identified.

Although examining the changes in microbial profile is interesting, it is important to remember that it is the collective function and characteristics of the gut microbiota that interact with the host, and that >1 microbe can occupy a particular ecological niche within their environment. Therefore, similar functions can be carried out by different microbiota structures and the same functional outcome could occur with different changes in microbiota. This particularly supports food as an effective intervention, because it can shift the microbial profile at all taxonomic levels and may also affect composition and function separately. The type and strength of the effect of diet on the gut microbiota will be determined by existing microbiota composition and function and the host phenotype, including interactions with immune function. Research needs to include examination of the gut microbiota function as well, using metabolomics and/or metagenomics techniques.

Research, in both humans and animals, into mechanisms of the MGBA will continue to help to elucidate the mechanisms by which the gut microbiota affect depression and anxiety symptoms, as well as other psychological and neurological effects. Food interventions have the dual benefit of a direct impact on gut and brain physiology and an indirect effect via the gut microbiota. With continued research investigating these aspects of the MGBA, we will further our understanding and make advances in obtaining a well-understood and well-guided holistic approach to treating and preventing anxiety and depression.

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