A review of dietary and microbial connections to depression, anxiety, and stress

Andrew M. Taylor & Hannah D. Holscher

To cite this article: Andrew M. Taylor & Hannah D. Holscher (2018): A review of dietary and microbial connections to depression, anxiety, and stress, Nutritional Neuroscience, DOI: 10.1080/1028415X.2018.1493808

To link to this article: https://doi.org/10.1080/1028415X.2018.1493808

Published online: 09 Jul 2018.
A review of dietary and microbial connections to depression, anxiety, and stress

Andrew M. Taylor¹, Hannah D. Holscher ²

¹Department of Food Science and Human Nutrition, University of Illinois, Urbana, IL, USA, ²Division of Nutritional Sciences, University of Illinois, Urbana, IL, USA

Objective: Pre-clinical evidence suggests that the gastrointestinal microbiota contributes to mood and behavior disorders. Among humans, diet quality and patterns, which also impact the gastrointestinal microbiota, have been linked to depression, anxiety, and stress. This review summarizes findings from clinical studies using dietary intervention to improve depression, anxiety, or stress and the role the gastrointestinal microbiota may have in these disorders.

Methods: A literature search was conducted using the keywords microbiome, microbiota, depression, anxiety, stress, diet, dietary pattern, diet quality, fiber, prebiotics, probiotics, and mood.

Results: Mood was improved by enhancing diet quality fructooligosaccharide and galactooligosaccharide improved anxiety and depression in participants consuming ≥ 5 g/day. Additionally, bifidobacteria were enriched in subjects consuming ≥ 5 g/day. Probiotic consumption improved psychological or biological measures of depression, anxiety, or stress in individuals predisposed to a mood disorder. Probiotics suppressed biological markers of stress in healthy individuals in a strain-dependent manner.

Discussion: High-quality diets, prebiotics, and probiotics may beneficially affect mood. Habitual diets rich in dietary fiber and omega-3-polyunsaturated fatty acids may be linked to reduced risk of developing symptoms of depression, anxiety, and stress; however, additional studies are necessary. Certain probiotics may enhance mood, but their influence on the gastrointestinal microbiota requires further investigation.

Keywords: Microbiome, Probiotics, Prebiotics, Fiber, Microbiota, Mood, Diet quality

Introduction

There is increasing evidence that the gastrointestinal microbiota influences human health, and metabolic, gastrointestinal, and psychological diseases.¹⁻³ Pre-clinical and clinical evidence suggest that the gastrointestinal microbiota influence mood and behavior, including depression, anxiety, and stress.⁴⁻⁵ Similarly, diet, eating behaviors, and consumption of fiber and prebiotic fibers affect the composition and metabolic functions of the human gastrointestinal microbiota.⁶⁻¹¹ Clinical research has revealed diet quality, as well as specific dietary components and dietary supplements aid in prevention or treatment of symptoms of depression, anxiety, and stress. Specifically, high diet quality, prebiotic fiber consumption, and probiotic supplements reduced anxiety symptoms and had anti-depressant effects in humans.¹²⁻¹⁵ The exact role the gastrointestinal microbiota play in the development of mental disorders is still being elucidated, but its involvement in bidirectional communication between the brain and gastrointestinal tract via the gut-brain axis is presumably a fundamental link between the microbiota and mood disorders. Delineating the relationship between diet, the gastrointestinal microbiota, and mental health is important for future applications of diet therapy for the treatment of depression, anxiety, and stress.

Herein, we review and discuss dietary and microbial factors that may influence the symptoms of depression, anxiety, and stress. The primary focus of this article is on the outcomes from dietary intervention trials conducted in human subjects.

Gut microbiota and mood

The brain-gut-microbiota axis is a bidirectional communication network that allows gastrointestinal microbes to convey information to the brain, and for the brain to communicate with the gastrointestinal tract. The mechanisms by which microbes affect mood in humans are not fully known, but pre-clinical studies have demonstrated that the gut microbiota plays an important role in mental health.⁵,¹⁶⁻¹⁸ For example, depression symptoms have been transferred via fecal microbiota transplant from depressed
The gut microbiota of depressed individuals have been compared to healthy individuals and alterations at several taxonomic levels were reported. Notably, differences in the dominant phyla, Bacteroidetes, Firmicutes, and Actinobacteria, were observed, but the relative abundances of these phyla were not consistent between the two studies. Jiang et al. reported increased relative abundances of Bacteroidetes and Actinobacteria, among others, and decreased relative abundances of Firmicutes. Zheng et al. similarly reported higher relative abundances of Actinobacteria; however, Bacteroidetes were lower, and no differences were observed in Firmicutes. Others have reported that Bacteroidetes is positively associated with depression. These conflicting results may, in part, be explained by a lack of control for diet as the aforementioned studies did not collect dietary data. As diet influences the gut microbiota, it may be contributing to the lack of consistency among trails.

To understand the mechanisms and impact the gut microbiota have on mood, additional clinical trials are needed. Future studies should examine the role of dietary intake and dietary components in altering gut microbiota of individuals with mood disorders. As we will discuss, dietary intervention has been reported to improve mood. However, human dietary interventions trials investigating the gut microbiota as a mediator of mood improvement are lacking.

**Diet quality and mood: observational studies**

Observational studies provide evidence linking poor diet quality to depression, while good diet quality has been connected to a reduced risk of depression. Recently, a nine-year prospective cohort study reported a lower risk of depression for subjects in the highest tertile of diet quality compared to the lowest tertile. The Mediterranean diet has also been associated with a reduced risk of depression among participants with high and moderate adherence to the Mediterranean diet pattern. Interestingly, the Mediterranean diet, and other dietary patterns rich in fruits and vegetables, have been shown to beneficially impact the gut microbiota. Dietary patterns aimed at reducing diet inflammatory potential have been also connected to a reduced risk of depression. Dietary recommendations to reduce the risk of depression include increasing the intake of fruits, vegetables, fish, whole-grains, legumes, and olive oil, in conjunction with reducing the consumption of highly refined grains, red meat, fried foods, and sweets.

The Mediterranean diet pattern has been connected to a reduced risk of depression presumably by altering pro-inflammatory mechanisms. The risk of developing depression has been linked to diets with high inflammatory potential, i.e. energy-dense foods, high-fat and high-sugar, refined grains, and alcohol. The inflammatory potential of a diet can be measured using a dietary index, e.g. Dietary Inflammatory Index, which categorizes an individual’s diet on a continuum ranging from maximally anti-inflammatory to maximally inflammatory. The Mediterranean diet pattern has a low inflammatory potential.

Systematic reviews and meta-analyses investigating the relationship between diet quality and depression have reported a relationship between measures of diet quality and depression. However, additional clinical intervention trials are needed to determine if there is a causal role of dietary factors on depression.

**Dietary components**

The habitual intake of specific food groups has been associated with stress and depression. Specifically, sweets and fast-food are consumed more frequently in stressed and depressed individuals. Contrarily, fruits and vegetables are consumed less frequently by depressed individuals.

Interestingly, the intake of dietary fiber derived from fruits and vegetables, but not total, soluble, or insoluble fiber intake, has been reported to be inversely related to depression symptoms. Dietary fibers comprise the cell walls of fruits and vegetables and are resistant to digestion by human enzymes, e.g. pectins, gums, and fructans, but may be metabolized by microbial enzymes in the gastrointestinal tract. Thus, these dietary fibers can be fermented by resident microbes, resulting in the production of short-chain fatty acids (SCFA). SCFA, especially butyrate, play a crucial role in regulating intestinal epithelial barrier integrity by providing energy to intestinal epithelial cells and microbes, and by stimulating the secretion of glucagon-like peptides 1 and 2. Glucagon-like peptides 1 and 2 decrease the permeability of intestinal epithelial cells. Inadequate dietary fiber intake deprives microbes of a nutrient source and decreases butyrate-producing bacteria. To compensate, secreted mucus glycoproteins may be used by microbes as an alternative energy source, eroding the colonic mucus barrier, and compromising intestinal barrier protection. A reduction in butyrate-producing bacteria may also compromise intestinal barrier protection. Accordingly, an increase in permeability allows the translocation of lipopolysaccharides, a component of the outer membrane of gram-negative bacteria and pro-inflammatory stimulus, into systemic circulation. Lipopolysaccharides play a significant role in chronic low-grade inflammation, a phenomenon known as endotoxemia. Inflammation is characteristic of...
depression.57 Thus, SCFAs may indirectly influence mood by modulating intestinal permeability and systemic lipopolysaccharide circulation.

In addition to providing a source of dietary fiber, fruits and vegetables are rich sources of antioxidants. Antioxidants play an important role in protecting cells from oxidative and nitrosative stress (ONS). ONS can damage cellular lipids, proteins, and DNA and cause cell death.58 ONS can also activate transcription factors, e.g. NF-κB, that lead to the expression of inflammatory cytokines.59,60 ONS and inflammation have been observed in depressed individuals.51,62 Dietary fiber and antioxidants are often consumed in low abundances in individuals following an unhealthy eating pattern.63 Antioxidants, e.g. polyphenols, may reach the large intestine in association with dietary fiber, and become dissociated when fiber is metabolized by colonic microbiota.54,65 Extraction, metabolism, and absorption of polyphenols from dietary fiber in the gastrointestinal tract are dependent on bacterial enzymes. Additionally, polyphenolics can modulate the gastrointestinal microbiota56,67 and act as antimicrobial or anti-inflammatory compounds.68–70 Thus, the elevated ONS and inflammation observed in depressed subjects may partially be explained by inadequate dietary intake of antioxidants.

**Diet quality and mood: clinical trials**

Clinical trials investigating the efficacy of dietary interventions to treat depression, anxiety, and stress have reported improvements in mood and behavior, and beneficial changes in biological markers (See Table 1). A common characteristic among diets improving mood was high unsaturated fatty acid or fiber intake.

The Mediterranean dietary pattern has been associated with a reduced risk of depression and has a low inflammatory potential.30–34 Recently, the Mediterranean diet with fish oil supplementation (900 mg/d docosahexaenoic acid and 200 mg/day eicosapentaenoic acid) improved mental health and quality of life scores in subjects with depression.71 This 6-month dietary intervention prescribed daily consumption of fish oil capsules, bi-weekly workshops that instructed participants on how to prepare and cook meals adhering to the Mediterranean diet pattern, a supply of food items specific to the recipes discussed during the workshops, and additional food items including extra-virgin olive oil, vegetables, fruit, canned legumes, canned tomatoes, canned tuna, and mixed nuts. Following three months of treatment, participants no longer attended bi-weekly workshops, but continued consuming fish oil supplements until the end of the trial. The control group did not receive any training or fish oil capsules but did attend ‘social workshops’ every two weeks. The social workshops consisted of various activities including playing games and book discussions, but did not include any nutrition or dietary advice or food items. Mental health outcomes were assessed by Depression, Anxiety, and Stress Scale (DASS) scores, Positive and Negative Affect Scale scores, and Assessment of Quality of Life-8D scale scores. After three months of participation in the study, the Mediterranean diet and control group improved all outcomes from baseline. However, the Mediterranean diet group’s DASS – Depression subscale scores and Assessment of Quality of Life-Mental health scores showed a greater improvement over the course of the study compared to the control group (1.68 and 1.52 times, respectively). No changes to outcomes from three months to six months were reported, despite similar Mediterranean diet scores between the two groups.

Adherence to a diet to reduce depression symptoms and nutritional counseling reduced symptoms of depression in subjects with major depression.12 Jacka and colleagues utilized nutritional counseling to provide support for diet quality and improve Montgomery–Asberg Depression Rating scale scores. They reported reductions in depression symptoms following personalized dietary support and counseling.12 The foundation of the treatment diet was modeled after the traditional Mediterranean diet, but also followed the recommendations of the Australian dietary guidelines and the Greek dietary guideline and was termed the ‘ModiMed’ diet. For a thorough description of the ModiMed diet see reference.72 Briefly, the ModiMed diet recommended daily intakes of wholegrains (5–8 servings), vegetables (6 servings), fruits (3–5 servings), reduced-fat and unsweetened dairy (2–3 servings), extra-virgin olive oil (60 mL), and nuts (1 serving) and weekly consumptions of legumes (3–4 servings), lean red meat (3–4 servings), fish rich in oil (≥2 servings), poultry (2–3 servings), eggs (≤6 eggs), and limit additional foods to <3, e.g. fast-food, sweets, 2 alcoholic beverages, etc. Notably, the ModiMed diet provided >20% of total energy from monounsaturated fatty acids and daily dietary fiber intake was approximately 50 g/day. The recommendation of 3–4 servings of lean red meat was substantiated by reports linking weekly intake of lean red meat outside the range of 3–4 servings to a greater likelihood of depressive and anxiety disorders and the richness of nutrients hypothesized to play a protective role in many mental illnesses, e.g. iron, zinc, and vitamin B12.72

Brinkworth et al. conducted a 1-year dietary intervention implementing a high carbohydrate/low-fat diet or a low carbohydrate/high-fat diet and reported reductions in Beck Depression Inventory scores and improvements to Profile of Mood States scores from both diets.73 The low carbohydrate/high-fat diet limited carbohydrates to 14% of total kilocalories and set the daily intake of fat at 58% of total energy;
Taylor and Holscher  A review of dietary and microbial connections to depression, anxiety, and stress

unsaturated fatty acids comprised 51% (38% monounsaturated fatty acids; 13% polyunsaturated fat (PUFA)) of this group’s diet. Diets rich in unsaturated fatty acids, especially long-chain PUFAs may have anti-depressant effects on depressed individuals.39,40 Similarly, the high carbohydrate/low-fat diet group’s fat consumption was primarily comprised of unsaturated fatty acids.

Similar results were reported in a clinical trial that investigated the effect of saturated fatty acid:unsaturated fatty acid ratio on mood and behavior.74 The saturated fatty acid, palmitic acid, and monounsaturated fatty acid, oleic acid, were given to participants at a ratio of either high palmitic acid:low oleic acid or high oleic acid:low palmitic acid. All food was provided to the subjects during the intervention.74

<table>
<thead>
<tr>
<th>Reference</th>
<th>Behavior studied</th>
<th>Population</th>
<th>Mood assessment tool</th>
<th>Design</th>
<th>Intervention</th>
<th>Duration</th>
<th>Behavioral outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>Depression, Anxiety, Mood, Well-being and self-efficacy</td>
<td>Moderate to severe depressed males and females</td>
<td>MADRS, POMS, HADS, CGH-I, WHO-5</td>
<td>Randomized parallel group, single blind, N=67; CON=34, TRT=33</td>
<td>Diet Support (personalized nutritional counseling sessions and advice; e.g. motivational interviewing, goal setting, and mindful eating.)</td>
<td>12 weeks</td>
<td>Diet may provide an efficacious treatment for common mental disorders.</td>
</tr>
<tr>
<td>71</td>
<td>Depression</td>
<td>Depressed males and females</td>
<td>DASS, AQoL, PANAS</td>
<td>Randomized, single blind N=152; CON=77, TRT=75</td>
<td>Fish oil supplement (900 mg DHA/ day and 200 mg EPA/ day) and 3 months of Mediterranean diet-style cooking workshops</td>
<td>6 months</td>
<td>DASS depression subscale improved greater than control and AQoL and PANAS improved from baseline</td>
</tr>
<tr>
<td>73</td>
<td>Psychosocial health</td>
<td>Obese, T2DM</td>
<td>POMS, BDI, SAI</td>
<td>Randomized N=115; TRT1=58, TRT2=57</td>
<td>Low Carb and High Carb diet, exercise 3x week</td>
<td>1 year</td>
<td>Improved quality of life measures, mood state in both diet groups</td>
</tr>
<tr>
<td>77</td>
<td>Depression, Anxiety, Mood, Well-being and Self-efficacy</td>
<td>Healthy weight, overweight, and obese male and females</td>
<td>POMS, CES-D</td>
<td>Randomized, crossover, controlled feeding N=82</td>
<td>Low-glycemic load (&lt;125 glycemic load/d) and high-glycemic load diet (&gt;250 glycemic load/d)</td>
<td>4 weeks</td>
<td>HGL resulted in 38% higher score for depressive symptoms on the CES-D; Overweight/obese had 40% higher scores on CES-D scale</td>
</tr>
<tr>
<td>74</td>
<td>Anxiety, Depression, and Mood State</td>
<td>Healthy, normal, overweight, and obese BMI</td>
<td>POMS</td>
<td>Randomized, double-blind, crossover N=32</td>
<td>Oleic acid:Palmitic acid; (40.29 g/ 100 g:30.95 g/ 100 g, respectively) Or (4.59 g/100 g:74.80 g/100 g, respectively) Omega-3-polyunsaturated fatty acids (2.5 g/ day; 2085 mg eicosapentaenoic acid and 348 mg/day docosahexaenoic acid)</td>
<td>3 weeks</td>
<td>Reduced anger hostility scores</td>
</tr>
<tr>
<td>75</td>
<td>Depression and Anxiety</td>
<td>Healthy, medical students</td>
<td>CES-D, BAI</td>
<td>Randomized, double-blind, parallel group N=68; CON=34, TRT=34</td>
<td>Omega-3-polyunsaturated fatty acids (2.5 g/ day; 2085 mg eicosapentaenoic acid and 348 mg/day docosahexaenoic acid)</td>
<td>12 weeks</td>
<td>Reduced anxiety scores, depression scores were unaffected</td>
</tr>
</tbody>
</table>

AQoL, Assessment of Quality of Life; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; CES-D, Center for Epidemiological Studies; CGH-I, Clinical Global Impression – Improvement; COPE, Copenhagen Burnout Inventory; DASS, Depression, Anxiety, and Stress Scale; DHA, Docosahexaenoic Acid; EPA, Eicosapentaenoic Acid; HADS, Hospital Anxiety and Depression Scale; MADRS, Montgomery-Asberg Depression Rating Scale; OSI, Occupational Stress inventory; PANAS, Positive and Negative Affect Scale; POMS, Profile of Mood States; PSS, Perceived Stress Scale; SAI, Spielberger State Anxiety Inventory; WHO-5, World Health Organization Well-being Scale; RCT, Randomized, Controlled Trial; CON, Control group; TRT, Treatment Group; T2DM, Type 2 Diabetes Mellitus; LC, Low Carbohydrate Diet; HC, High Carbohydrate Diet
Utilizing the Profile of Mood States questionnaire, Kien et al. reported a reduction in subscale scores related to anger-hostility among subjects receiving high oleic acid compared to high palmitic acid treatment. In men, high oleic acid treatment corresponded with a decrease in total mood disturbance.

The supplementation of omega-3-PUFAs may also confer mental health benefits, although mixed results have been reported. Kiecolt-Glaser and colleagues compared omega-3 PUFAs to a placebo mimicking the saturated:monounsaturated:polyunsaturated fatty acid ratio consumed by US adults. Compared to controls, subjects in the treatment group exhibited a 14% reduction in lipopolysaccharide-stimulated pro-inflammatory cytokine interleukin-6 (IL-6) and a 20% reduction in anxiety symptoms. Additionally, they reported n-6 PUFA:n-3 PUFA ratio as a slightly stronger predictor of anxiety scores and lipopolysaccharide-stimulated IL-6 production with increasing n-6 PUFA:n-3 PUFA ratio associated with increased anxiety scores and lipopolysaccharide-stimulated IL-6 production.

In 2016, Breymeyer et al. reported differences in mood between a high-glycemic load diet and low-glycemic load diet. The dietary fiber content of the low-glycemic load diet was consumed compared to the high-glycemic load diet. Moreover, participants consuming a high-glycemic load diet reported higher Profile of Mood States subscale scores, fatigue/inertia and total mood disturbance, indicative of lower subjective energy and less mood stability. Clinical Epidemiological Studies Depression Scale scores were 38% higher when a high-glycemic load diet was consumed compared to when a low-glycemic load diet was consumed. The investigators reported lower mean vigor/activity scores, a subscale of the Profile of Mood States questionnaire, during the high-glycemic load diet compared to the low-glycemic load diet. Moreover, participants consuming a high-glycemic load diet reported higher Profile of Mood States subscale scores, fatigue/inertia and total mood disturbance, indicative of lower subjective energy and less mood stability. Clinical Epidemiological Studies Depression Scale scores were 38% higher when a high-glycemic load diet was consumed compared to when a low-glycemic load diet was consumed. The results suggest glycemic load impacts subjective mood. Specifically, high-glycemic load diets may decrease subjective energy perception, while reducing mood stability.

The improvement in Beck Depression Inventory scores and total mood disturbance scores may be related to the high unsaturated fatty acid content of the treatments. Unsatuated fatty acids may improve depression symptoms by reducing systemic inflammation. Unsaturated fatty acids are involved in multiple signaling pathways, and their inhibition of pro-inflammatory cytokines may be related to the therapeutic effects exerted by unsaturated fatty acid consumption. Individuals with depression have been shown to have high concentrations of circulating pro-inflammatory cytokines. Additionally, saturated fatty acids can elicit an inflammatory response by acting on pro-inflammatory receptors, e.g. toll-like receptor 4.

Dietary fat intake can also influence the gastrointestinal microbiota and inflammation, see reference for a more thorough review. Briefly, dietary fat intake stimulates the secretion of bile acids. Bile acids that reach the large intestine have an antimicrobial effect on resident microbes. Gram-negative bacteria, a primary source of lipopolysaccharides, tend to be more tolerant of bile acids compared to gram-positive bacteria. Thus, high dietary fat intake may reduce total bacterial numbers in the large intestine, while the proportion of gram-negative bacteria are enhanced, increasing a major source of lipopolysaccharides. However, it is important to note that the direct effect dietary fats have on the gut microbiota is still not well known, largely due to the incorporation of fat at the expense of carbohydrates, a major source of energy for microbes, in study diets.

The evidence provided from clinical trials suggests diet quality impacts mood. It should also bring attention to dietary fiber and n-3-PUFAs consumption. The relationship between fiber and mood is less explored than n-3-PUFAs. However, both may improve mood by reducing systemic inflammation. Intervention trials are needed to determine if fiber consumption contributes to changes in mood and if the food source of fiber or the isolated fiber by itself affects mood.

**Prebiotic fibers and gastrointestinal microbiota**

A prebiotic is a substrate that is selectively utilized by host microorganisms conferring a health benefit to the host. Most prebiotics are fibers, however, it is not a prerequisite for being considered a prebiotic. As research continues, it is likely that additional dietary components, such as polyphenols, may be recognized as prebiotics. Prebiotics are present within foods, e.g. onions, chicory root, and wheat, or taken in a purified form as a dietary supplement. Prebiotics may attenuate disease by promoting the growth of beneficial microbes and/or reducing pathogenic microbes. Prebiotics have demonstrated psychobiotic effects in human clinical trials. Psychobiotic describes a bacteria or source of support for bacteria that beneficially affects the relationship between the microbiota and brain. Commonly studied prebiotics for mood and behavior improvement include fructooligosaccharides and galactooligosaccharides. Both prebiotics have demonstrated the ability to enhance *Bifidobacterium* in humans. Although, the bifidogenic effect may be dose-dependent, requiring ≥5.0 g/day to enhance bifidobacteria. Bifidobacteria may promote health benefits by producing B vitamins, antioxidants, and polyphenols; and aiding immune system function by inducing the production of immunoglobulins. Additionally, bifidobacteria contribute to the production of lactate and acetate, which can be utilized
by other bacteria in the gastrointestinal microbial community to produce butyrate, a phenomenon known as cross-feeding. This production of SCFA also provides a benefit to the host by suppressing pathogenic microbes by the inherent decrease in pH with increasing SCFA concentrations.

Prebiotics and mood: clinical trials

Three randomized controlled trials (Table 2) reported improvements in mood or behavior following the consumption of prebiotic fibers, fructooligosaccharides, galactooligosaccharides, or trans-galactooligosaccharides. Fructooligosaccharides and trans-galactooligosaccharides supplemented at 5.0 and 7.0 g/day, respectively, induced changes to the gastrointestinal microbiota, along with improvements in mood.

Silk et al. examined the ability of trans-galactooligosaccharide to relieve symptoms of irritable bowel syndrome and improve mood. Patients receiving 7.0 g/day of trans-galactooligosaccharide reported significantly lower scores on the Hospital Anxiety and Depression Scale-Anxiety subscale compared to baseline. Trans-galactooligosaccharide enhanced Bifidobacterium spp. and reduced Clostridium perfringens subgroup histolyticum, Bacteroides/Prevotella ratio, and Eubacterium rectale/Clostridium coccoides.

Similar results have been reported following fructooligosaccharide consumption. A study investigating the efficacy of 5 g/day fructooligosaccharide to treat irritable bowel syndrome reported a decrease in Hospital Anxiety and Depression Scale-Anxiety subscale scores. Moreover, fructooligosaccharide consumption increased fecal bifidobacteria.

In 2015, Schmidt et al. assessed the effects of Bimuno® galactooligosaccharide and fructooligosaccharides on salivary cortisol levels and emotional processing. They reported anxiolytic-like effects and decreased waking salivary cortisol concentrations and attentional vigilance to negative versus positive stimuli in subjects receiving Bimuno® galactooligosaccharide treatment. No differences in salivary cortisol were reported for the fructooligosaccharide treatment.

The anxiolytic and anti-depressant effects demonstrated in these trials are not well-understood and additional studies are needed to confirm the anxiolytic and anti-depressant effects of specific prebiotics. One explanation for the changes in mood may be related to the bifidogenic effect from fructooligosaccharide and galactooligosaccharide supplementation. Prebiotics fermented by microbes in the gastrointestinal tract produce metabolites, like SCFA, that may enhance and help regulate immune system function. Dysregulation of the immune system may disrupt homeostasis, altering critical feedback mechanism, e.g. cortisol production.

Table 2: Clinical intervention trials investigating prebiotics and mood

<table>
<thead>
<tr>
<th>Reference</th>
<th>Mood Assessment Tool</th>
<th>Population</th>
<th>Intervention (Dose)</th>
<th>Duration</th>
<th>Behavioral Outcome</th>
<th>Microbiota Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>101</td>
<td>HADS</td>
<td>Healthy adults</td>
<td>scFOS (5.0 g/day)</td>
<td>4 weeks</td>
<td>Improved anxiety and depression</td>
<td>Increased Bifidobacterium in both placebo and control</td>
</tr>
<tr>
<td>100</td>
<td>FERT, ECM</td>
<td>Healthy adults</td>
<td>FOS or BGOS (5.5 g/day)</td>
<td>3 weeks</td>
<td>Increased attentional vigilance to negative versus positive information following BGOS</td>
<td>n/a</td>
</tr>
<tr>
<td>15</td>
<td>HADS</td>
<td>IBS patients</td>
<td>TGOS (3.5 or 7.0 g/day)</td>
<td>12 weeks</td>
<td>Improved anxiety</td>
<td>Increased bifidobacteria ratio; 7.0 g/day of prebiotic decreased Bacteroides:Prevotella ratio</td>
</tr>
</tbody>
</table>

CON, Control Group; ECM, Emotional Categorization and Memory; ETB, Emotional Processing Task; FERT, Facial Expression Recognition; GCS, Galactooligosaccharides; HADS, Hospital Anxiety and Depression Scale; scFOS, Short-chain Fructooligosaccharide; TRT, Treatment Group; TGS, Trans-galactooligosaccharides.
Cortisol, a glucocorticoid hormone, has widespread effects and is involved in several mechanisms of homeostasis and adaption to stressors, such as glucose metabolism, immune system regulation, and inflammation. A key regulator of cortisol production is the hypothalamic–pituitary–adrenal (HPA) axis. The HPA axis primarily regulates cortisol output through negative feedback mechanisms, but stressors, e.g. inflammation and psychological stress, can bypass these control mechanisms and increase HPA axis activity resulting in increased cortisol production. Chronic exposure to stressors cause over-suppression of the immune system, increased circulating pro-inflammatory cytokines, and increased risk of developing anxiety and depression. Gastrointestinal microbiota may mediate HPA activity by modulating immune responses to stressors.

Probiotics and mood

Probiotics, defined as live microorganisms that when consumed in adequate amounts confer health benefits to the host, have demonstrated benefits to mental health (Table 2). Probiotics are inherent in many fermented foods, e.g. yogurt, sauerkraut, and kefir, and are commercially available as dietary supplements. Probiotic consumption can promote gastrointestinal microbiome functions, including inhibition of pathogenic species, epithelial barrier integrity, and modulation of immune response. Probiotics, specifically, Lactobacillus spp. and Bifidobacterium spp., are typically representative of only a small proportion of the human gastrointestinal microbial community but have been associated with improvements in mental health. A probiotic strain may affect mood by direct or indirect interaction with the central nervous system, modulation of immune response, and inhibition of opportunistic pathogens.

Gastrointestinal microbes can interact with the central nervous system directly or indirectly through the synthesis of neurotransmitters, e.g. serotonin, and metabolites that interact with hormone receptors in the large intestine; SCFA activate GPR43 on L-cells stimulating the release of glucagon-like peptide-1. Serotonin and its precursor, tryptophan, can be produced by microbes in the gastrointestinal tract and may influence the concentration of serotonin in the brain. Low levels of serotonin in the brain have been associated with depressed mood. The influence microbially derived neurotransmitters have on psychophysiology is still being researched, but modulation of neurotransmission of the enteric nervous system may contribute to the release of gut hormones linked to mood and behavior.

Probiotics and mood: clinical trials

Studies investigating the effect of single-strain probiotics on mood have reported improvements in humans, Table 3. For example, Bifidobacterium longum species may promote improvements in mental health. B. longum strains have been shown to reduce stress and depression scores. Additionally, Messaoudi and colleagues reported decreased Hospital Anxiety and Depression Scale scores in participants consuming a probiotic comprised of B. longum R0175 and Lactobacillus helveticus R0052.

Clinical trials investigating L. casei Shirota have reported reductions in anxiety scores and biomarkers of stress in subjects consuming the probiotic. L. casei Shirota consumption reduced anxiety scores in individuals suffering from chronic fatigue syndrome. In a cohort of medical students preparing for an exam, where self-reported stress increased as the exam approached, consumption of L. casei Shirota suppressed stress-response genes. Additionally, salivary cortisol was elevated in the placebo-treatment, but not in subjects consuming probiotic treatment, as the exam approached. However, these findings were not replicated in healthy individuals. Benton et al. reported null findings following the consumption of a milk-drink containing L. casei Shirota in healthy adults. Thus, L. casei Shirota may suppress stress and anxiety rather than reducing it.

It is also important to note that the probiotic effects of bacteria are strain dependent. For example, two different strains of Lactobacillus, L. rhamnosus JB-1 and L. rhamnosus HN001, were used in separate studies. Kelly and colleagues administered L. rhamnosus JB-1 to healthy adult men and women and reported no differences in physiological or psychological measures of stress. Conversely, women consuming L. rhamnosus HN001 from ~15 weeks gestation to 6 months post-partum reported lower depression and anxiety scores compared to placebo.

Multi-strain probiotics have also demonstrated the ability to improve mood (see Table 3) in healthy and diseased populations. Although many of the multi-strain probiotics improved mood, outcome measurements were not consistent when probiotics containing the same species of bacteria were consumed. For example, Steenberg et al. investigated a probiotic containing B. bifidum, L. acidophilus, and L. casei among others, and reported no changes to Beck Depression Inventory scores. Contrarily, Akkakesh et al. reported a reduction in Beck Depression Inventory scores following the consumption of a probiotic containing the same three bacterial species. These conflicting results may partially be explained by the differences in study populations, as Akkakesh and
colleagues studied the probiotics affect on subjects suffering from major depressive disorder. Moreover, the dose of probiotic administered in the study conducted by Steenberg et al was lower than the dose prescribed by Akkakesh et al. To fully understand the effects probiotics have on mood, additional intervention studies need to be conducted in healthy and diseased populations and the prescribed dosages of the probiotic and strain should be similar to past studies.

**Limitations of clinical trials**

**Diet quality**

A limitation of dietary trials is that adherence to a prescribed dietary pattern is frequently measured by self-reported diet records or self-reported questionnaires. Self-reported diet records may not accurately reflect the amount of food consumed by a participant resulting in under- or overestimated values. It is also not always possible, or is very difficult, to blind participants and/or researchers to nutritional treatments, which may bias results. In addition, the impact dietary changes have on the gastrointestinal microbiota was not measured by any of the clinical trials investigating diet quality and mood in this review. Thus, we can only speculate on the role gastrointestinal microbiota played in the mood and behavioral changes.

**Prebiotics**

Fructooligosaccharides and galactooligosaccharides demonstrated anxiolytic effects when 5.0 g/day or more was consumed. However, only one study was conducted in healthy adults. The other two studies reported findings from patients with irritable bowel syndrome. Many of the trials reviewed also lacked participant dietary information. Additional studies in healthy populations are needed to translate these results to the general population.

**Probiotics**

A majority of the studies investigating the effects of probiotics on mood and behavior reported improvements. However, few studies analyzed the gastrointestinal microbiota. Also, to better understand an individual strain’s therapeutic effect, additional studies with single-strain probiotics need to be conducted as the utility of a probiotic may depend on the strain. Investigating the gastrointestinal microbiota will also provide insight into the adoptions occurring in the gastrointestinal ecosystem following probiotic consumption. Microbiota analyses may help differentiate responders versus non-responders to probiotic treatment in future studies.

**Summary of findings**

Consumption of high-quality diets reduced depression, anxiety, and stress symptoms in clinical trials, especially when intervention diets were rich in n-3-PUFAs and fiber. Furthermore, fiber from fruits and vegetables was associated with reduced likelihood of depression symptoms, irrespective of total fiber intake. This may partially be explained by the high concentrations of antioxidants within fruits. Fiber and antioxidants may synergistically benefit gut health by enriching bifidobacteria and reducing inflammation.

Galactooligosaccharide and fructooligosaccharide consumption had anxiolytic and anti-depressive effects on subjects with irritable bowel syndrome. When they were administered to healthy women, galactooligosaccharides induced anxiolytic effects in the participants. Notably, a reduction in waking cortisol was reported in a healthy cohort of women, but no significant reduction in anxiety scores was observed in self-reported questionnaires. Although specific prebiotics have displayed psychobiotic properties, due to the very limited evidence available, additional clinical intervention studies are needed before they can be accepted as anxiolytic or anti-depressive.

The clinical trials investigating probiotics revealed certain probiotics were efficacious as therapeutic agents for the treatment of depression, anxiety, and stress. Both physiological biomarkers and psychological symptoms were relieved or suppressed following the consumption of probiotics. Specifically, *B. longum* and *L. casei* Shirota may have therapeutic effects for individuals suffering from mood disorders.

**Conclusions**

Reports from dietary interventions provide evidence that there is a link between diet quality and mood. Yet, the directionality of these relationships still needs to be discerned. To accomplish this, longitudinal studies and clinical trials need to be conducted and biological markers of disease need to be recorded. The efficacy of prebiotics to treat mood disorders is less certain due to a paucity of studies investigating prebiotics effect on mood. Regarding the gastrointestinal microbiota, altered microbiota composition has been reported in depressed individuals and specific microbes have been associated with depression, but an insufficient amount of clinical data is currently available to causatively link the gastrointestinal microbiota to depression, anxiety, and stress in humans. Additional well-designed dietary intervention trials targeting the interconnection of diet quality, dietary components, and the gastrointestinal microbiota are required. Identifying the microbial species residing in the gastrointestinal tract will help progress our understanding of their involvement in mood disorders. Nevertheless, microbiota compositional data has a limited capacity to characterize microbiome functionality. Thus, additional multi-omics technologies are
<table>
<thead>
<tr>
<th>Reference</th>
<th>Behavior Studied</th>
<th>Population</th>
<th>Mood Assessment Tool</th>
<th>Design</th>
<th>Intervention (Dose)</th>
<th>Duration</th>
<th>Behavioral Outcome</th>
<th>Microbiota Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>114</td>
<td>Depression and Anxiety</td>
<td>IBS patients, Mild to moderate anxiety and/or depression</td>
<td>HADS, STAI</td>
<td>Randomized, double-blind, placebo-controlled, N=44; CON=22, TRT=22</td>
<td><em>Bifidobacterium longum</em> NCC3001 (1×10^10 cfu/day)</td>
<td>6 weeks</td>
<td>Reduced depression but not anxiety</td>
<td>Null</td>
</tr>
<tr>
<td>113</td>
<td>Depression, Anxiety, Stress</td>
<td>Healthy males</td>
<td>CSS</td>
<td>Crossover, placebo-controlled, N=22</td>
<td><em>Bifidobacterium longum</em> 1714 (1×10^9 cfu/day)</td>
<td>4 weeks</td>
<td>Reduced stress and improved memory</td>
<td>n/a</td>
</tr>
<tr>
<td>115</td>
<td>Depression, Anxiety, Stress, Coping Strategies</td>
<td>Healthy adults</td>
<td>HADS, PSS</td>
<td>Randomized, double-blind, placebo-controlled, parallel group, N=55; CON=29, TRT=26</td>
<td><em>Lactobacillus helveticus</em> R0052, <em>Bifidobacterium longum</em> R0175 (3×10^9 cfu/day)</td>
<td>30 days</td>
<td>Decrease in cortisol values, Decrease in HADS-D scores</td>
<td>n/a</td>
</tr>
<tr>
<td>118</td>
<td>Anxiety and Stress</td>
<td>Healthy adult medical students</td>
<td>STAI</td>
<td>Randomized, double-blind, placebo-controlled, parallel group, N=149</td>
<td><em>Lactobacillus casei</em> Shirota (100×10^11 cfu/day)</td>
<td>8 weeks</td>
<td>Treatment did not reduce anxiety scores. Salivary cortisol levels were significantly lower in the treatment group compared to placebo.</td>
<td>n/a</td>
</tr>
<tr>
<td>117</td>
<td>Stress</td>
<td>Healthy adult medical students</td>
<td>STAI</td>
<td>Randomized, double-blind, placebo-controlled, parallel group, N=47</td>
<td><em>Lactobacillus casei</em> Shirota (100×10^11 cfu/day)</td>
<td>8 weeks</td>
<td>Maintained salivary cortisol levels from baseline in the treatment group; a twofold increase in expression of stress-response genes in placebo compared to treatment</td>
<td>Alpha-diversity was maintained; <em>Bacteroidaceae</em> family was significantly lower before the exam compared to placebo</td>
</tr>
<tr>
<td>116</td>
<td>Depression and Anxiety</td>
<td>Chronic fatigue syndrome patients</td>
<td>BDI, BAI</td>
<td>Randomized, double-blind, placebo-controlled, pilot study, N=35</td>
<td><em>Lactobacillus casei</em> Shirota (24×10^9 cfu/day)</td>
<td>8 weeks</td>
<td>Reduced anxiety scores compared to control</td>
<td>Lactobacillus and <em>Bifidobacterium</em> increased from baseline</td>
</tr>
<tr>
<td>119</td>
<td>Mood</td>
<td>Healthy adults</td>
<td>POMS</td>
<td>Randomized, double-blind, placebo-controlled, parallel group, N=124</td>
<td><em>Lactobacillus casei</em> Shirota (65×10^8 cfu/day)</td>
<td>3 weeks</td>
<td>No effects</td>
<td>n/a</td>
</tr>
<tr>
<td>126</td>
<td>Anxiety and Stress</td>
<td>IBS, undergraduate medical students</td>
<td>HADS, STAI</td>
<td>Double-blind, placebo-controlled, parallel group, N=69; CON=35, TRT=34</td>
<td><em>Lactobacillus gasseri</em> CP2305 (1×10^10 cfu/day)</td>
<td>12 weeks</td>
<td>Improved sleep quality, normalized bowel habits under stressful situations</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Continued
<table>
<thead>
<tr>
<th>Reference</th>
<th>Behavior Studied</th>
<th>Population</th>
<th>Mood Assessment Tool</th>
<th>Design</th>
<th>Intervention (Dose)</th>
<th>Duration</th>
<th>Behavioral Outcome</th>
<th>Microbiota Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>121</td>
<td>Depression and Anxiety</td>
<td>Pregnant women through post-partum</td>
<td>EPDS, STAI</td>
<td>Randomized, double-blind, placebo-controlled $N=380$; CON = 187; TRT = 193</td>
<td>Lactobacillus rhamnosus HN001 $(1\times 10^9 \text{cfu/day})$</td>
<td>~15 weeks gestation + 6 months post-partum</td>
<td>Lower post-partum depression and anxiety scores compared to control</td>
<td>n/a</td>
</tr>
<tr>
<td>120</td>
<td>Depression, Anxiety, and Stress</td>
<td>Healthy males</td>
<td>MINI, SECPT</td>
<td>Randomized, placebo-controlled, crossover $N=29$</td>
<td>Lactobacillus rhamnosus JB-1 $(1\times 10^9 \text{cfu/day})$</td>
<td>8 weeks</td>
<td>No effects</td>
<td>Null</td>
</tr>
<tr>
<td>125</td>
<td>Major Depressive Disorder</td>
<td>MDD</td>
<td>BDI</td>
<td>Randomized, double-blind, placebo-controlled $N=40$; CON = 20, TRT1 = 25, TRT2 = 20</td>
<td>Lactobacillus acidophilus, Lactobacillus casei, Bifidobacterium bifidum $(2\times 10^9 \text{cfu/day of each bacteria})$; Probiotic capsule: <em>Lactobacillus casei</em> $(3\times 10^3 \text{cfu/day})$, <em>L. acidophilus</em> $(3\times 10^9 \text{cfu/day})$, <em>L. casei</em> $(7\times 10^9 \text{cfu/day})$, <em>L. rhamnosus</em> $(5\times 10^9 \text{cfu/day})$, <em>Bifidobacterium breve</em> $(5\times 10^9 \text{cfu/day})$, <em>Bifidobacterium lactis</em> $(2\times 10^7 \text{cfu/day})$, <em>B. longum</em> $(1\times 10^9 \text{cfu/day})$, <em>Streptococcus thermophilus</em> $(3\times 10^8 \text{cfu/day})$, <em>Lactobacillus acidophilus</em> W52, <em>Bifidobacterium lactis</em> W56, <em>Bifidobacterium breve</em> W63, <em>Bifidobacterium lactis</em> W52, <em>Streptococcus thermophilus</em> W23, <em>Lactobacillus acidophilus</em> W37, <em>Lactobacillus brevis</em> W63, <em>Lactobacillus casei</em> W56, <em>Bifidobacterium lactis</em> W24, and <em>Lactococcus lactis</em> (W19 and W58) $(6\times 10^9 \text{cfu/day})$</td>
<td>6 weeks</td>
<td>Improved DASS scores with either probiotic treatment</td>
<td>n/a</td>
</tr>
<tr>
<td>123</td>
<td>Reactivity to Sad Mood</td>
<td>Healthy adults</td>
<td>LEIDS-r, BDI-II</td>
<td>Randomized, triple-blind, parallel group $N=40$; CON = 20, TRT = 20</td>
<td>Lactobacillus rhamnosus HN001 $(1\times 10^9 \text{cfu/day})$, <em>Bifidobacterium bifidum</em> $(2\times 10^9 \text{cfu/day})$, <em>Streptococcus thermophilus</em> $(3\times 10^8 \text{cfu/day})$, <em>Bifidobacterium lactis</em> W52, <em>Lactobacillus acidophilus</em> W37, <em>Lactobacillus brevis</em> W63, <em>Lactobacillus casei</em> W56, <em>Bifidobacterium lactis</em> W24, and <em>Lactococcus lactis</em> (W19 and W58) $(6\times 10^9 \text{cfu/day})$</td>
<td>4 weeks</td>
<td>Reduced overall cognitive reactivity to sad mood</td>
<td>n/a</td>
</tr>
</tbody>
</table>
null

References


15 Silk DBA, Davis A, Vulevic J, Tzortzis G, Gibson GR. Clinical trial: The effects of a trans-galactooligosaccharide prebiotic on needed to develop an understanding of mechanisms and pathways the microbiota may alter.

Disclaimer statements

Contributors Both authors wrote and approved the final manuscript.

Funding This work was supported by the USDA National Institute of Food and Agriculture, Hatch project under Grant number 1009249.

Conflicts of interest The authors report no conflict of interest.

Ethics approval Not applicable.

ORCID

Hannah D. Holscher http://orcid.org/0000-0003-4918-2426


77 Kien CL, Bunn JY, Tompkins CL, Dumas JA, Crain KI, Bunn JY, Tompkins CL, Dumas JA, Crain KI.
80 Kiecoli-Glaser JK, Velury MA, Andridge R, Malarkey WB, et al. The inhibitory effect of polyphenols on modula...


