

# Eating for Happiness – *New Mechanisms for the Role of Nutrition in the Prevention of Depression*

## Introduction

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It is becoming well-known that the food we eat profoundly impacts mental health and the development of mental illnesses, including depression.<sup>1-5</sup> It is also known that depression is an inflammatory condition.<sup>3-9</sup> However, less is known about inflammation in the brain and how it may play a role in depression. Depression is a debilitating health issue that affects an astounding number of people at approximately ~322 million people worldwide,<sup>10</sup> including 1 in 12 Americans.<sup>11</sup> Persons with depression experience a significantly reduced quality of life, with symptoms such as low self-worth, loss of pleasure, fatigue, and sleeplessness. Depression can also lead to suicide.<sup>10</sup> Anxiety disorder is another common and related illness, as one in five people experience either anxiety or depression in any given year.<sup>12</sup> Even for those without clinically diagnosed mental illnesses, symptoms of depression and anxiety are prevalent across the general population.<sup>13</sup> Due to the high economic cost from lost productivity and increased demand on healthcare services, mental health issues incur immense burden for both the person and the society.<sup>14</sup>

Another problem that may occur alongside depression is substance use disorder (SUD), which is a growing crisis worldwide.<sup>15</sup> Drug addiction involves a compulsion to seek and take drugs, a loss of control, and withdrawal symptoms (e.g. depression and anxiety) when drug use is discontinued.<sup>16</sup> It has become a critical public health issue, as the number of drug overdose deaths rose from approximately 17,000 in 1999 to near 70,000 in 2017. Recent estimates suggest that 130+ people in the United States die from an opioid overdose every day.<sup>17</sup> What remains baffling is that this high number of deaths still occur even with an abundance of treatment centers available. Today's mental health treatments typically involve drug and psychological therapies, often neglecting the profound role that nutrition and lifestyle play in mental wellness.<sup>18,19</sup> Estimates suggest 15–30% of people with depression resist current medications and some believe this contributes to relapse.<sup>20</sup> Meanwhile, it has been suggested that only one-third of patients with depression completely heal with anti-depressants and other medications, as these medications only exert moderate effects and do not address the root causes of the condition.<sup>20-22</sup>

There is an urgent need for strategies that are cost-effective, low-risk, and easy to implement in daily life. Our current treatments for mental health conditions may be useful in the short-term but may be insufficient for the long-term. There are new mechanisms related to gastrointestinal function currently being elucidated that may prove useful in treating mental health conditions. There is a need to better understand the role of inflammation in mental illness in order to treat it most effectively with diet.<sup>15</sup> It has been shown that unhealthy diets can harm our mental health, but the mediators of this relationship have been difficult to establish. Is the food we eat linked to the inflammation that occurs in depression? Is it possible that gastrointestinal inflammation travels to the brain? Would this impact mental health for some people more than others? Emerging research has shown that it is a clear yes, yes, and yes. There's also growing evidence that nutrition impacts the gut microbiome to influence brain inflammation and the development of mental illness.<sup>20</sup> This article will review recent evidence of the ways that diet impacts our mental health due to its association with neuroinflammation<sup>23</sup>. The authors will also suggest the direction that mental illness treatment centers and healthcare professionals should consider in efforts to relieve mental illnesses, including depression, anxiety, and SUD.

## Neuroinflammation and Mental Illness

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**Inflammation overview.** To determine how inflammation travels to the brain, whole body inflammation must be understood first. Inflammation is a natural, beneficial function of the immune system that signals danger in order to protect us from further harm, such as injuries and diseases.<sup>24,25</sup> For example, inflammation can appear as red bumps on the skin after we get bitten by insects. This indicates that we should take care of ourselves to prevent getting bitten again and to avoid touching inflamed areas to prevent further irritation. However, excess inflammation is harmful,

especially in mental health where instead of physical symptoms, it presents as painful emotions and potentially irrational behaviors. Inflammation can be assessed in the blood as high levels of inflammatory substances which damage the brain directly, including cytokines, interleukins, Tumor Necrosis Factor-alpha (TNF- $\alpha$ ),<sup>15,26</sup> and C-Reactive Protein (CRP).<sup>27,28</sup> Through this understanding of inflammation, current literature has revealed mechanisms of how it can travel to regions of the brain and cause neuroinflammation.

**Neuroinflammation.** Neuroinflammation occurs when our brain immune cells, called microglia, are activated and release inflammatory cytokines and reactive oxygen species that directly cause brain damage.<sup>29</sup> It can also occur when cytokines are made elsewhere in the body and travel to the brain through active transport and ‘leaky’ regions across the blood-brain barrier. Cytokines can worsen mental health by interacting with neurotransmitters to negatively alter brain signaling patterns,<sup>30</sup> generate behavioral changes, and contribute to mood disorders.<sup>23</sup>

**“Happy” hormone disruption.** The depletion of our “happy” hormones and neurotransmitters, serotonin and dopamine, is one way that neuroinflammation can compromise mental health. Cytokines can reduce the production of serotonin<sup>31,32</sup> to induce depressive moods.<sup>33</sup> Excess cytokine release along with oxidative stress in neuroinflammation can also disrupt dopamine action to result in its depletion.<sup>34</sup> This can be highly detrimental as healthy dopamine signaling is needed for regulating social behavior and preventing depression.<sup>35-37</sup>

The important role of dopamine may be observed in those with autism spectrum disorder (ASD). Neuroinflammation downregulates dopamine signaling in these individuals, resulting in decreased pleasure gained from socialization and reduced motivation to interact with others. This disruption of the dopaminergic system can occur for not only those with ASD, but for all who experience neuroinflammation.<sup>38</sup> Hence, it was no surprise when studies found that healthy adults given cytokines had depressive symptoms compared to those given a placebo.<sup>39-41</sup> Additionally, evidence has shown that the high cytokine levels found in persons with Parkinson’s disease and Alzheimer’s disease could be responsible for cognitive dysfunction and depressive symptoms. Hence, neuroinflammation is a hallmark feature of both mental illness and brain disorders.<sup>42,43</sup>

**Mitochondrial derived inflammation.** One way that brain inflammation can arise is through mitochondrial dysfunction. When our mitochondria (energy-producing organelles) are damaged, inflammation occurs. This damage can be caused by stressors including psychological pain and a poor diet, which cause the release of an inflammatory molecule called circulating cell-free mitochondrial DNA (ccf-mtDNA) from mitochondria into the bloodstream. Inflammatory foods associated with the poor-quality Western diet (e.g. refined carbohydrates and certain vegetable oils) can trigger this leakage of ccf-mtDNA out of cells by increasing oxidative stress. The ccf-mtDNA then travels via the circulatory system to the brain, causing neuroinflammation. As inflammatory responses in mental illnesses involve mitochondrial signaling, reducing mitochondrial damage is vital to reducing neuroinflammation and preventing depression.<sup>44</sup>

**Inflammation from drug abuse.** Another source of neuroinflammation is substance abuse, as many drugs render the brain more susceptible to inflammation and therefore mental illness. Drugs including methamphetamine, cocaine, and alcohol<sup>16</sup> can directly promote neuroinflammation by increasing cytokine production in the brain. This results in brain toxicity and the inhibition of healthy neuronal activity which makes the neuroinflammation become increasingly injurious.<sup>45</sup> The resulting brain dysfunction can promote further addiction-related activities, for example, chronic cocaine use has been shown to prompt inflammatory signaling that drives further cocaine seeking.<sup>46</sup>

**Treatments.** Currently, anti-inflammatory medications such as statins and non-steroidal anti-inflammatory drugs (NSAIDs) are used to reduce the behavioral and cognitive consequences of mental illnesses and brain disorders<sup>47</sup>. Unfortunately, these medications only target the downstream effects of inflammation and not the source<sup>30</sup>. These medications may also result in undesirable side effects, including increased neurotoxicity.<sup>15</sup> Thus, we urgently need treatments that exert beneficial anti-inflammatory actions with a low risk of adverse effects, such as dietary improvement. It is crucial to focus on diet, as neuroinflammation has been found to result from unhealthy eating patterns. Harmful nutrients from poor-quality diets can drive this inflammation by shifting metabolic pathways, leading to an imbalance in substances that are critical to optimal brain functioning.<sup>48</sup> Unraveling the mechanisms of

how inflammatory foods behave in our body might show the detrimental effects they have on our mental health and well-being.

## Nutrition and Neuroinflammation

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Dietary patterns have changed substantially worldwide over recent decades. The Western diet has been associated with excess consumption, and replacement of traditional, less-processed diets, with highly processed foods.<sup>49</sup> This has occurred in the past few decades due to dramatic agricultural changes regarding dairy products, fried and processed foods containing vegetable oils, and red meat. Hence, the Western diet comprises of high intakes of saturated fats, added sugars, and refined starches from these foods.<sup>50</sup> These pro-inflammatory substances increase the severity of symptoms in depression, anxiety, and other mental illnesses as they directly increase inflammation<sup>51</sup>. This way of eating has been catastrophic to population health, as it results in a state of preventable inflammation<sup>52-55</sup>. It also has a shockingly drastic impact on mental health, so it is vital to look at the nutrients involved and how they act in the body to illustrate potential links between nutrition and neuroinflammation.

**Fatty acids in neuroinflammation.** Recent research has shown the colossal impact that nutrients have on neuroinflammatory processes which alter our brain chemistry. These nutrients include fatty acids, which act as signaling molecules to regulate brain function. However, the overconsumption of saturated fatty acids in the Western diet stimulates increased inflammatory responses in microglia,<sup>23,56</sup> leading to brain inflammation, cognitive impairment, and the potential development of mood disorders.<sup>57-60</sup> Another inflammatory component of this diet is the over-consumption of omega-6 fatty acids, while neglecting the consumption of omega-3 fatty acids.

Anti-inflammatory omega-3 fats are powerful in lowering disease risk,<sup>61-64</sup> and are abundant in fatty fish, nuts, seeds, legumes, and leafy greens<sup>65,66</sup>. These fats also play a role in regulating emotions and increase our ability to cope with stress. The increased intake of omega-6 fatty acids to the exclusion of omega-3 fatty acids has resulted in an imbalance of these fats. This is prevalent in populations of all Western countries.<sup>67</sup> As omega-3 and omega-6 fats make up 35% of the fats in the brain<sup>68</sup> and compete for the same metabolic pathways, their balance is important to brain function and reducing inflammation.<sup>69,70</sup> These findings suggest that the type and amount of fat we eat can heavily influence the magnitude of inflammation and depression.

**Nutrient deficiencies drive neuroinflammation.** Neuroinflammation and depression can arise from deficiencies of nutrients and beneficial bioactive substances that are needed for brain function.<sup>71-73</sup> These substances include selenium, lycopene, magnesium, vitamin B-6, iron, and vitamin D. Low intakes of these nutrients and others has been associated with greater inflammation, depression, and anxiety.<sup>53, 74-78</sup> For example, a low Vitamin B-6 status has been linked to mental distress, as B-6 is essential for making dopamine and serotonin.<sup>79,80</sup> Also, a low vitamin D status may disrupt sleep regulation, hormone production, brain cell growth,<sup>81</sup> and immune responses.<sup>82</sup> As vitamin D receptors are expressed in key areas of the brain, dietary vitamin D (rich in fish and eggs) can reduce neuroinflammation and prevent disease progression.<sup>83</sup> This potent, anti-inflammatory nature of vitamin D was demonstrated in persons with cystic fibrosis who had decreased cytokine levels after vitamin D treatment.<sup>84</sup> Nutritional diversity and optimal micronutrient status are needed to reduce neuroinflammation. This can be achieved by eating various nutrient-dense foods to help mitigate mental illness and brain disorders.<sup>85-88</sup>

**Anti-inflammatory diets support mental health.** Extensive research has found that a high-quality diet reduces neuroinflammation, as the foods in this diet contain various anti-inflammatory nutrients. For example, increased choline intake (high amounts in eggs, broccoli, and cauliflower) and whole-grain consumption have been associated with lower cytokine levels.<sup>89-92</sup> Whole-grains are beneficial to reducing inflammation and depression as they're rich in beta-glucan fibers that promote a healthy immune system<sup>93</sup> and gut microbiome.<sup>94</sup> They are also phytochemical-rich, which helps to dampen the oxidative stress that results from inflammation.<sup>95</sup> Many other nutrient-rich foods that are abundant in a high-quality diet have also been found to exert beneficial properties to our overall health. These anti-inflammatory foods include vegetables, fruit, fish, legumes, and poultry.<sup>96</sup> What's most advantageous about these dietary patterns is that there's a strong evidence base indicating their mechanisms in supporting mental health.

A meta-analysis involving over 100,000 participants clearly showed that an antioxidant-rich diet prevents and reduces depressive symptoms. Antioxidants are fundamental contributors to a healthy diet's anti-inflammatory power<sup>97,98</sup> as they reduce the amounts of inflammatory reactive oxygen species (ROS) that are released in the body during food metabolism. Antioxidants can even limit and reverse the inflammatory responses to meals rich in saturated fat. With this reduction of inflammation, it is not surprising antioxidants have been shown to reduce depression and anxiety. Thus, consuming a varied, nutrient-rich diet appears promising in reducing neuroinflammation and mental illness.<sup>99</sup>

## Neuroinflammation and the Microbiome

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While food components can directly stimulate neuroinflammation, could invisible life forms also be involved? Emerging research has shown that nutrients can influence neuroinflammatory responses by interacting with gut bacteria.<sup>23</sup> Dietary interventions involving anti-inflammatory nutrients have been found to reduce neuroinflammation and the risk of depression by enhancing gut microbiome health.<sup>100</sup> Hence, the gut microbiota should be targeted to improve brain health and alleviate mental illness.

**Gut microbiome overview.** The human body is permanently colonized by microbes, with most of them residing in the gut.<sup>101</sup> Around 100 trillion of these gut bacteria live in harmony with our bodies as they're needed to regulate many functions. For example, these bacteria control the activity of immune cells in the intestine and brain to regulate gut motility, neuroinflammation, mood, and behavior.<sup>102,103</sup> As gut bacteria can make a direct impact on brain activity by producing neurotransmitters, inflammatory molecules, and hormones,<sup>104,105</sup> they may have an important role in influencing mental health<sup>106</sup>. What's crucial about the gut microbiome is that it is not a single bacterial species that can dictate our health, but instead the overall gut microbial composition. All substances we consume can alter this composition, whether it be food, drink, or even opioids, as they interact with bacteria in the gut. This means the development of neuroinflammatory diseases, including depression, is influenced by our gut health, which in turn is shaped by our food choices.<sup>107</sup>

**Gut-brain axis.** What we put in our body plays a profound role in our mental health due to "gut-brain axis" bidirectional mechanisms. The gut-brain axis describes the constant communication between the gut microbiome and the brain that occurs through the vagus nerve.<sup>108</sup> Gut bacteria recruit this axis or connection route to modify brain activity, and in return, the brain responds to influence gut activity.<sup>109,110</sup> The gut-brain relationship can become defective when we expose our microbiota to stress, resulting in microbial composition changes. This can stimulate neuroinflammatory signaling from bacteria to promote brain dysfunction.<sup>111,112</sup>

An example of a major gut stressor is an unhealthful diet, which can heighten our susceptibility to depression.<sup>113</sup> Hence, the gut microbiomes of those who eat a Western diet have a very different composition from those of people who eat more healthfully. Those consuming the highly processed Western diet may be missing or have reduced protective microbes while they shelter more pathogenic microbes that may contribute to their disease symptoms.<sup>114</sup> This was demonstrated when mice that had gut microbial transplantation from persons with depression showed anxious and depressive symptoms, while the mice colonized with microbes from those without depression did not exhibit these symptoms.<sup>115,116</sup> This could have been due to the production of metabolites from a disturbed microbiome, which entered the circulation through a "leaky gut" and reached the brain to result in neuroinflammation.<sup>113</sup>

**Leaky gut.** In normal conditions, immune cells that make cytokines are located separately from gut bacteria. In a condition of leaky gut (increased gut permeability) which can be triggered by an unhealthful diet,<sup>117,118</sup> the protective barrier between the gut and the bloodstream is damaged. Toxins and undigested food can then leak out of the gut into the circulatory system.<sup>119</sup> An example of a toxin is lipopolysaccharide (LPS), which is higher in an imbalanced microbiota that co-occurs with leaky gut. When these LPS molecules leak into the blood, they potently stimulate the production of inflammatory cytokines.<sup>120</sup> This leak into the bloodstream can then result in behavioral changes as the molecules travel to the brain to cause neuroinflammation.<sup>121-123</sup> The LPS molecules also increase the production of

ROS which exacerbates inflammation<sup>124,125</sup> and increases depression risk.<sup>47</sup> Consequently, leaky gut could be a primary factor in mental illness development.<sup>126</sup>

**Fiber and gut health.** A low-quality diet can also perpetuate inflammation as it is low in fiber, which reduces microbial diversity and supports fewer disease-fighting bacteria.<sup>107</sup> Additionally, an unhealthful diet contains excess added sugars, artificial sweeteners, and emulsifiers from processed foods which can alter the gut microbiome to activate inflammatory pathways.<sup>127</sup> Therefore, it is clear that a poor-quality diet has devastating impacts on our gut and mental health.<sup>128</sup> In contrast, a healthful diet high in fiber and phytonutrients can prevent and potentially resolve brain dysfunction, depression, and anxiety, and ultimately enhance one's quality of life.

One mechanism of action is through the wide variety of bioactive substances obtained from a high-quality diet which can have beneficial interactions with gut bacteria.<sup>129-131</sup> For example, fruits and vegetables are rich in polyphenols which can reduce depression due to their anti-inflammatory and neuroprotective properties.<sup>132,133</sup> A healthy dietary pattern would also have probiotics and other bioactive components that can be protective from mental illness.<sup>134,135</sup> These components help to facilitate our feelings of happiness and heal brain structure by efficiently regulating serotonin signaling and supporting gut health.<sup>136</sup> This highlights the importance of a healthy diet in restoring beneficial microbes to alleviate leaky gut, brain inflammation, and mental illness.

## Treating Neuroinflammation and Depression with Nutrition

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With all these mechanisms, it may seem terrifying that the foods many eat regularly or treat ourselves to can impact our mental health. It is important to have the awareness that what you put in your body manifests in far more ways than only your appearance. While this evidence could be deflating, knowing that the brain alterations occurring in depression and other mental illnesses are to a large extent *preventable*. Albeit slower than medications, nutrition and other lifestyle changes may lead to improvement in symptoms and/or resolution!<sup>47</sup> As a healthful diet has been linked to lower depression rates and suicide risk,<sup>130</sup> the integration of nutrition in psychiatric care is critical for the prevention and reduction of symptoms in depression, anxiety, and SUD.<sup>18</sup> This makes it vital to examine how anti-inflammatory dietary strategies target the neuroinflammatory pathways in individuals living with mental illnesses.<sup>137</sup>

**High-quality diet overview.** The brain is an energy-intensive organ that relies on a continuous, nutritive supply of macro- and micronutrients from our diet<sup>138</sup> to powerfully influence mental health. Meta-analyses have concluded that nutrient-dense diets can elevate moods and reduce symptoms of mental illness. These diets typically include whole foods and are predominantly plant-based along with fatty fish or lean meats of choice.<sup>139,140</sup> While there are specific foods identified in a high-quality diet, it is important to know that there is no single food that individually improves brain health. It is the synergistic combination of various nutrient dense foods that exerts impressive effects. Numerous studies point to Mediterranean style diets for the treatment of mental illnesses,<sup>141-143</sup> but the focus should not be on following a specific diet. Instead, the emphasis should be on setting a foundation that is full of anti-inflammatory, nutrient dense, and minimally processed foods. Individuals can then customize this broad yet nourishing dietary pattern to their preferences.

**Nutrition for a healthy gut and mind.** Supporting bacteria within a healthy gut microbiome through nutrition has also been found to be highly effective in preventing and treating depression. It is recommended that treatment centers should encourage the consumption of probiotic-containing fermented foods (such as sauerkraut and dairy or non-dairy yogurts) along with complex carbohydrates (grains and starchy vegetables), fruit, and non-starchy vegetables.<sup>144</sup> These plant foods have a dramatic impact on gut microbiota, as dietary fiber and carbohydrates are important determinants of microbial composition.<sup>106</sup> Specifically, gut bacteria use soluble fibers (such as oats, sweet potatoes, lentils, nuts, seeds, and peas) for fermentation. This results in the production of short-chain fatty acids (SCFAs), including acetate and butyrate. As butyrate is anti-inflammatory, it stops the production of cytokines in the brain to prevent and reverse neuroinflammation.<sup>145</sup> This suggests that a diet high in soluble fiber could improve mental health by increasing SCFA-producing bacteria in the gut.<sup>146</sup>

**Dietary coaching.** Beyond the nutritive value of food, interventions including nutrition coaching may improve and/or prevent depressive symptoms as effectively as medication and behavioral therapy. Nutrition coaching is a cost-effective, personalized, and medication-free intervention for improving mental health.<sup>147-150</sup> Nutrition coaching may include nutrition counseling, nutrition education, cooking demonstrations, and online social support<sup>20</sup>. A robust nutrition coaching strategy would also encourage mindful eating while removing the pressure of caloric restriction and weight loss. It is important to avoid succumbing to today's diet culture, as eating healthy foods, if done restrictively, could exacerbate depressive symptoms. Another factor of healthy eating is that it involves, not only the nutrition profile of the foods consumed, but also whether there are positive emotions and mindfulness associated with eating them. Successful interventions involving these components are detailed in Table 1.

Group nutrition therapies may help to reduce depression risk by encouraging social interactions and other forms of healthy mental stimulation. This can occur within the group setting, as well as outside treatment sessions when individuals eat meals with friends and loved ones at home. Socializing is a beneficial mental activity that increases energy flow into mitochondria to enhance brain cell function and regulate mood. When cell function is optimized, inflammation is reduced and more mitochondria are produced in the brain,<sup>44</sup> which is highly supportive of mental health. Therefore, socializing in a long-term dietary support group could significantly improve symptoms of mental illness.

**Population health approaches.** One suggestion, to raise awareness of nutritional impacts on brain inflammation and mental health, is to make this topic a compulsory subject in the educational system and public health programs. Beyond academic settings, dietetic and healthcare professionals can contribute by showing others credible dietary tips for depression treatment, such as the online hand-out created by the Behavioral Health Nutrition Dietetic Practice Group of the Academy of Nutrition and Dietetics.<sup>151</sup> As it is clear that we now have a growing number of credible resources and evidence, we must encourage everyone to become well-informed about the link between nutrition and mental health to alleviate global suffering.

## Conclusion

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Based on current findings, a strong approach to mental illness treatment includes a combination of nutrition guidance, therapy, and loving presence through social support.<sup>129</sup> Nutrition is one of the most vital parts of everyone's lives, yet it is frequently overlooked in mental health treatment. There are potential solutions, but not enough is being done with them. Many treatment centers have not integrated nutrition into their approaches for the prevention and treatment of depression and other mental illnesses. Although we do not know how every mechanism occurs within the interplay between neuroinflammation, depression, and nutrition, the recent influx of high-quality studies suggest its growing importance. These studies have consistently demonstrated the dangerous inflammatory effects of a poor-quality diet, which can predispose individuals to mental illnesses and brain disorders. The studies have also shown the positive effects of healthful diets on depressive symptoms. Given the gravity of depression and its co-morbid illnesses, it is imperative that we prioritize nutrition interventions that will end the pandemic of declining mental health.

Research advancements remain futile until we take action on them and implement nutritional therapies in psychiatric care. We suggest a holistic approach that combines our current therapeutic strategies with nutrition for a truly effective solution. For this reason, it is essential that all healthcare practitioners have basic nutritional knowledge. Some may want to shift focus from medication to nutrition in order to be more holistic. Collaboration with dietitians for nutrition coaching may be a promising and cost-effective treatment for persons with mental illness.

Supporting access to group-based nutrition programs should also be a policy priority. The allocation of funds to this solution is essential for our country to realize the potential benefits of reducing depression risk.<sup>56</sup> Mental illness isn't a choice, it is a disease. If we neglect the best treatment approach possible for the hundreds of millions who suffer when we already have answers, where does that leave humanity? Let's lead the way for change.

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## Intervention Details

**Table 1.** Selected nutrition interventions promoting a high-quality diet in the treatment of mental illness.

Study	Intervention	Control	No. of Participants	Participant Condition	Intervention Frequency	Intervention Delivery Mode	Key Findings / Recommendations
Jenkinson et al., 2009 <sup>149</sup>	RCT: <i>Diet intervention and knee strengthening exercise</i>	Advice leaflet only	289	BMI $\geq$ 28 and knee pain	Visits over 2 years (1 per month for 1 <sup>st</sup> 6 months, then every other month for remaining months)	Home visits by a dietitian, dietetic assistant, and research interviewer	Home-based program of individualized dietary advice and knee exercises in overweight and obese individuals reduced depression and knee pain.
McMillan et al., 2011 <sup>150</sup>	RCT: <i>Diet intervention</i>	No diet change	25	Healthy, young female adults			The Mediterranean diet improved moods and cognition without portion control.
O'Neil et al., 2013 <sup>18</sup>	Randomized control trial (RCT): <i>Diet intervention and nutrition consulting</i>	Social support	176	Major depressive episodes	7 sessions (1 hr each)	Individual, in person by a dietitian	Group receiving dietary guidance became self-sufficient in making healthier and cheaper food choices. Therefore, they had substantially reduced societal and healthcare costs than those who only received social support.
Agarwal et al., 2015 <sup>148</sup>	Quasi-experimental study: <i>Workplace nutritional therapy and social support</i>	No instruction	292	BMI > 25 or type 2 diabetes	18 sessions (1 hr each, 1 per week)	Group, in person by a dietitian, physician, and cooking instructor	Plant-based dietary therapy and coaching improved depression, anxiety, and productivity in a workplace setting.
Bersani et al., 2017 <sup>142</sup>	Clinical trial: <i>Nutrition and mental health education</i>	Mental health education only	32	Mood or psychotic disorder	5 sessions (~1.5 hrs each, 1 per week)	Group, in person	Nutrition and mental health education together were more effective in improving depressive symptoms and sleep quality than only mental health education.

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