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A Targeted Nutrition Protocol for the Prevention and Treatment of Depression: A Systematic Review of the Evidence

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Abstract

Rates of depression have been rising steadily over the last several decades with more than 264 million people affected, making it one of the top three burdens globally. The pandemic has brought on a greater risk of depression. Forty-two percent of individuals surveyed in December 2020 by the US Census Bureau reported depressive symptoms. Many factors, including poor diet quality, play a role in the development of depression during traumatic events like the pandemic. A low-quality dietary pattern has been associated with obesity, low-grade chronic inflammation, dysbiosis, increased cortisol levels and monoamine neurotransmitter deficiency. Among others, these factors have been correlated with an increased risk of depression. Additionally, antidepressants have been shown to be ineffective in up to 40% of individuals. Therefore, the potential of a nutrition-focused approach could be helpful. A systematic review was conducted to determine if an evidence-based, targeted nutrition protocol could be developed for the prevention or treatment of depressive symptoms. The results of nearly 100 studies strongly indicate certain nutrients and dietary patterns have the potential to reduce depressive symptoms.

Keywords: Depression, nutrition protocol, dietary pattern, depressive symptoms, anti-inflammatory, monoamine neurotransmitters

Introduction

Depression affects more than 264 million people globally making it one of the top three global burdens of disease.[1] As of 2020, it is the leading cause of disability worldwide and the second cause of disability in the US for individuals under the age of 60.[1,2] Rates have been rising steadily over the last decades partially due to the increased intake of ultra-processed foods along with high intake of unhealthy fats, red meat and sweets.[3] Now, an even greater increase in rates of depression are being observed from the social isolation, personal loss, and socioeconomic instability brought on by the COVID-19 pandemic.[4] Early in the pandemic, rates of depressive symptoms had increased to 27.8%, in comparison to the 8.5% prior to the pandemic.[5] As of December 2020, 42% percent of individuals surveyed by the US Census Bureau reported symptoms of depression compared to 11% in January 2019.[6] The rapid increase in incidence indicates a need to improve the way depression is currently being approached.

Many factors, including poor diet quality, play a role in the development of depression during traumatic events like the pandemic. Pham et al. surveyed over 8,200 individuals and found a reduced level of diet quality during quarantine increased the likelihood of depression.[7] Some studies found a greater increase in snacking and overall food intake amongst overweight and obese individuals during the pandemic.[8] Higher BMI was also associated with a lower intake of fruit, vegetables and legumes,[8] indicating a potentially lower diet quality. Overweight and obesity are considered a risk factor for depression because the systemic inflammation often associated affects the parts of the brain that help regulate mood and emotions.[9] In fact, data from a large sample study found that obesity was associated with an increased risk of depression.[10] Over 1 in 3 people worldwide are considered overweight or obese putting a large portion of the population at potential

risk.[2] In addition, studies have found that depression increases during and after a traumatic event indicating that the rates of depression could continue to rise in the coming years.[5]

Statistics show more individuals are consuming a Western-style diet which is correlated with an increased risk of depression.[3] It has been demonstrated that a diet with greater consumption of ultra-processed foods, red meat, sweets, unhealthy fats and a lower consumption of fruits, vegetables, legumes and whole grains, is positively correlated with increased risk of depression.[3] This unhealthy dietary pattern has been correlated with low-grade chronic inflammation as evidenced by an increase in pro-inflammatory markers like IL-6, IL-2, and CRP.[11] Contrastingly, a healthy dietary pattern is associated with increased levels of brain-derived neurotrophic factor (BDNF) and anti-inflammatory markers.[12] BDNF is a key molecule involved in neuroplasticity, and decreased levels have been associated with depression.[13]

The modulation of these pro- and anti-inflammatory proteins can occur in the gut microbiome. The gut microbiome and how it may affect neurophysiological states has only recently been discovered. This vast and complex system is composed of 10^{14} microorganisms making it more diverse than the human genome.[14] A diverse and dense microbiome has been found to associated with a decreased risk of disease, whereas a less diverse or disrupted balance, also known as dysbiosis, is found to be associated with an increased risk of disease including depression.[14-16]

The bidirectional communication between our enteric nervous system and central nervous system via the vagus nerve is known as the gut brain axis (GBA).[17] Disruption to the GBA can influence changes in gut microbiota composition, while modification of the microbiome can induce depressive-like behavior. Alteration of the microbiome composition can promote gaps in the endothelial lining of the gut increasing intestinal permeability leading to a leaky gut. This can

cause the translocation of certain Gram-negative bacteria, which can activate the immune system leading to a pro-inflammatory response.[11] Elevated levels of IgM and IgA in response to these circulating bacterial lipopolysaccharides (LPS) have been found in depressed individuals.[18] Additionally, a high ratio of omega-6 to omega-3 is also often reported in adults with depression.[19] Western diets are characterized by a ratio of omega-6 to omega-3 of approximately 15:1, indicating a low intake of omega-3 and an excessive intake of omega-6.[19]

Another characterization of the Western diet is a low intake of dietary fiber.[20] Fiber is an essential component of a healthy diet because it is fermented by the bacteria in the gut creating an abundance of short-chain fatty acids (SCFAs), which are thought to be the primary mechanism of metabolic interactions between the microbiota and host.[20] SCFAs have also been shown to help maintain gut endothelial integrity and reduce immune response inflammation.[21] Additionally, SCFAs have been found to play a role in modulating the Hypothalamus-Pituitary-Adrenal axis (HPA axis) activity.[22] The HPA axis is a feedback loop involving the hypothalamus, pituitary gland, and adrenal glands. The dysregulation of this axis can be caused by the continuous output of cortisol, which can be stimulated by chronic stress, processed foods, and sugar.[23] Studies have found that high glycemic diets are associated with an increase in cortisol levels.[24] Consistently high levels of cortisol have been shown to increase intestinal permeability over time.[25]

Finally, the health of the microbiome can play a significant role in the synthesis of monoamine neurotransmitters. The monoamine hypothesis proposes the deficiency or depletion of serotonin, norepinephrine or epinephrine in the CNS is associated with depression.[26] A diet deficient in certain nutrients, such as vitamins B6, B9, and B12, can impact synthesis of these neurotransmitters.[27,28] Many antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are designed to increase

monoamine neurotransmission. While antidepressant use has been shown to increase neurotransmitter levels within days, impact on depressive symptoms is found to take weeks or longer.[29] Nevertheless, antidepressants are found to be ineffective in up to 40% of individuals with over half of individuals that continue taking antidepressants not fully entering remission.[30] This indicates that a deficiency in monoamine neurotransmitters is not the only factor in the pathophysiology of depression, but instead likely includes a unique combination of multiple factors.

Nutrition is one modifiable factor that can increase risk of depression and has been shown to strongly influence an individual's susceptibility to disease. Therefore, this systematic review will focus solely on the nutritional interventions that have been studied with regard to depression. Although multiple pathways or dysregulation of these pathways can play a role, dietary consumption of all essential nutrients that are part of the etiology of depression is necessary. Thus, the goal of this review is to determine if a targeted nutrition protocol can be developed for the prevention or treatment of depression.

Methods

This systematic review was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines and PICOS framework.[31,32]

- Participants (P) = all adults aged 18+
- Interventions (I) = dietary pattern, nutrient, supplement, herb, spice
- Comparisons (C) = habitual diet, placebo
- Outcomes (O) = reduction in depressive symptoms
- Study Design (S) = systematic review

The purpose of this review is to gather the evidence regarding nutrition intervention studies related to potential treatment or prevention of depression. Can a targeted nutrition protocol be developed from this evidence?

An electronic search was conducted using PubMed for its relevant inclusion of nutrition, health and science-related topics. Terms were searched in June 2021 and include: "nutritional intervention" OR "nutrition intervention" OR "nutrition protocol" OR "nutritional protocol" OR "diet intervention" OR "nutrition psychiatry" OR "nutrition therapy" AND "depression" AND "cross-sectional" AND "cohort" AND "randomized control trial". This review includes published studies with full text available, randomized control trials, clinical trials and observational studies in peer-reviewed journals in the English language with human adults. Inclusion criteria consisted of dietary pattern or nutrition intervention, depression outcome reported, and similar group treatment. Exclusion criteria consisted of low quality methodology, intervention period of less than 3 weeks, interventions that are not feasible or multiple intervention factors such as exercise, targeted weight loss (calorie restriction), missing both depression-specific screener and depression-specific outcome, pregnant or lactating women. A date range restriction of 2005 or later was imposed for all included studies. Joanna Briggs Critical Appraisal quality checklists were utilized by appropriate study type.[33]

Results

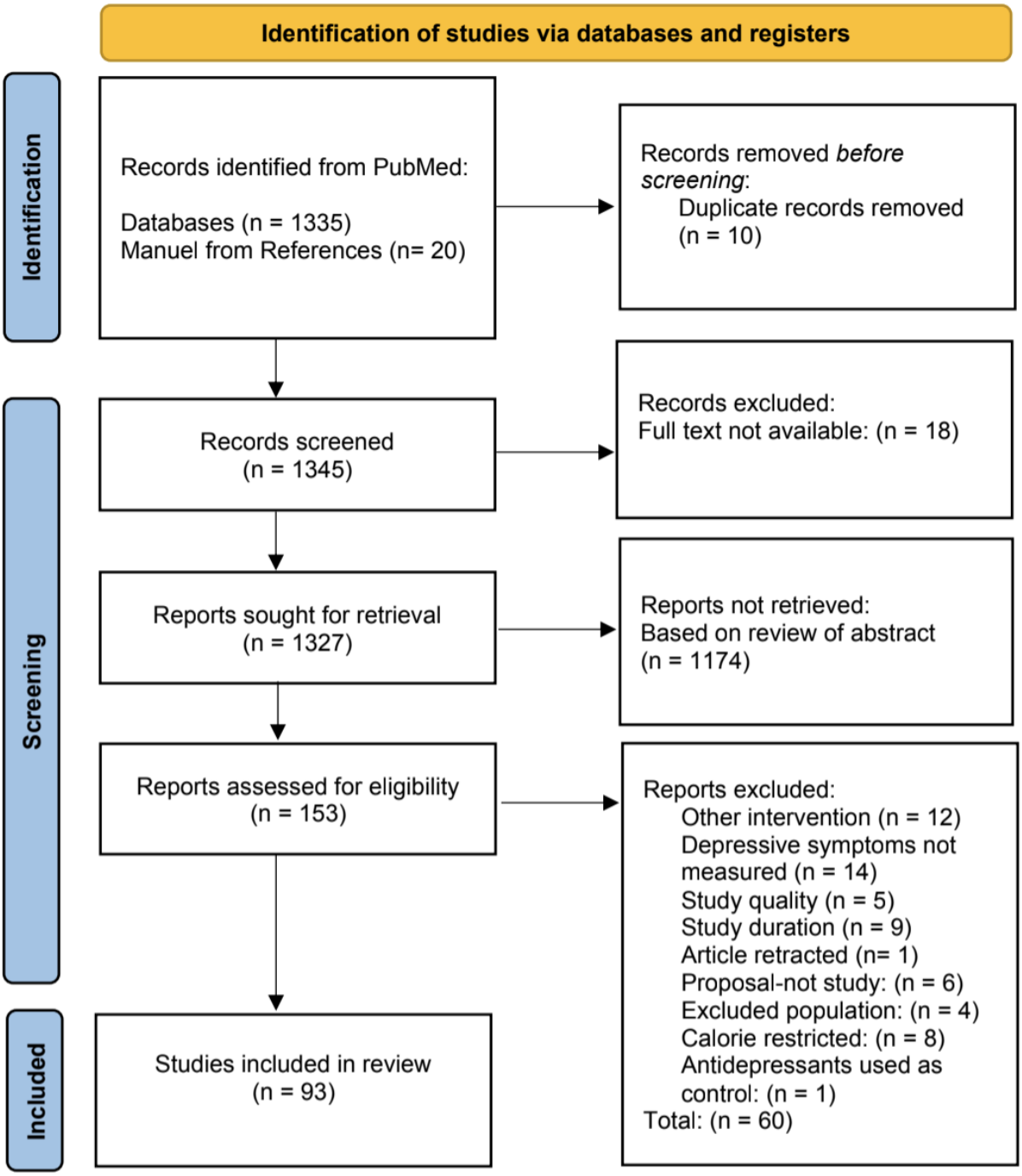

Figure 1. PRISMA 2020 flow diagram of systematic review search

Literature Search Summary

Our initial searches resulted in 1355 records and screening by title and abstract resulted in 153 relevant studies eligible for full-text review. After reviewing full articles, a total of 60 articles

were excluded due to duplicate studies, other interventions, depressive symptoms not reported or measured, study length too short for dietary impact, article quality or retraction, full text not available, proposals without intervention, excluded population, moderate calorie restriction, and antidepressants used as an intervention. Of the remaining studies, 93 met the quality criteria and were included.

Results: Dietary Pattern

Study Characteristics Dietary Patterns Summary

Table 1 is attached as a PDF document.

Primary Study Findings by Dietary Pattern

Table 2 is attached as a PDF document.

Mediterranean-style diet

All four randomized control trials (RCT) found a reduction in depressive symptoms with three studies showing significant in comparison to the control group.[34-37] However, in the additional study a 40% reduction in depression risk was found in the subgroup of Type 2 diabetes mellitus (T2DM) participants that consumed a Mediterranean diet with nuts, which was significant in comparison to the low-fat diet control group.[37]

Between the four observational studies, which included over 35,000 participants adherence to a Mediterranean-style diet was inversely associated with lower depression scores.[38-41] Sanchez-Villegas et al found over a 30% reduction in depression risk across subgroups, while Sakrupski et al reported a 98% decrease in depression risk in the highest tertile of adherence.[39,41]

Polyphenol & Flavonoid

One RCT with a polyphenol-rich diet intervention found a significant reduction in depressive symptoms as measured by the Depression Inventory-II (BDI-II) tool as compared to a low-polyphenol diet.[42]

Three observational studies found an inverse relationship with polyphenol or flavonoid intake, but results were only significant for individual components.[43-45] In one study flavones and anthocyanins were both found to be significantly associated in a dose-dependent manner.[43] Additionally, quercetin and naringenin were significantly associated in the highest quartile of intake.[43] Chang et al found a significant 18% reduction in depressive symptoms in individuals with the highest consumption of citrus. Also, individuals with the highest consumption of tea had a 12% significantly lower risk of depression.[45]

Low Protein

In two RCT studies, an increase in depressive symptoms was found during a low-protein regimen.[46,47] The increase was found to be higher when the LPD diet was consumed seven days per week compared to six.[46]

Chronic Disease Management Dietary Pattern

One RCT implemented a diabetes management dietary pattern intervention with training including management of diabetes.[48,49] A reduction in depressive symptoms was found in the diabetes management groups compared to controls.[48] A second RCT compared a vitality diet (VD) to a healthy dietary pattern (HD) for diabetes management. The VD contained low sodium and a higher intake of potassium and magnesium along with higher fruit and vegetable intake in comparison to the HD. The VD showed a reduction in depressive symptoms, but not significantly more than the control group.[49]

Healthy Dietary Pattern

Francis et al conducted a 21-day study with an intervention of a healthy diet, as defined by the Australian Guide to Healthy Eating. The RCT found a significant reduction in depressive symptoms in the intervention group compared to participants that consumed their habitual diet.[50]

Eleven observational studies found an inverse relationship between diet quality and lower depressive symptoms.[51-61] Rahmani et al found an 80% lower risk of depression in individuals with the highest Alternative Healthy Eating Index (AHEI-2010) scores as compared to the lowest adherence.[52] Saneei et al found participants in the highest quartile of AHEI-1020 had a 45% reduced risk of depression when compared to the bottom quartile.[53] An additional observational study found an association of well-balanced meals and daily milk product consumption to be associated with reduced depressive symptoms in both men and women. Avoidance of excess salt and fat were also correlated with reduced depression in men.[61]

Healthier Dietary Pattern

Ho et al conducted an RCT with a diet intervention to reduce consumption of red meat to less than five times per week and refined grains less than two times per day. The intervention group had a significant decrease in level of depression at twelve and twenty-four months.[62] Another RCT with a healthier dietary pattern, intended for weight loss, found a significant decrease in depression scores. Additionally, the healthier diet group had a significant change in microbial diversity along with increase in fiber, vegetable and milk consumption as compared to the control group.[63]

One observational study found reduced depressive symptoms correlated with higher adherence to a healthy Japanese-style dietary pattern, characterized by high intake of fruit, vegetables, mushrooms and soy.[64] Akbaraly et al observed a pattern of reduced depressive symptoms in participants in the highest tertile of whole food pattern as compared to processed

food pattern.[65] An additional observational study found intake of vitamin A, B6, C, folate, thiamine, riboflavin, Na, K, Mg, Ca, Fe, Zn and fiber was lower in depressed individuals.[66]

Plant-Based Dietary Pattern

Argarwai et al conducted a quasi-experimental study across five sites. A low-fat plant-based diet intervention was found to be associated with a significant reduction in depressive symptoms.[67]

Glycemic Index

A crossover design RCT found a significantly lower depression score with a low glycemic load (LGL) diet. Consumption of a high glycemic load (HGL) diet was found to have a 38% higher depression symptom score.[68] Additionally, an observational study of over 93,600 women found a higher glycemic index diet was associated with an increased risk of incident depression.[69]

Fish Consumption

Two observational studies found an inverse relationship between moderate fish consumption and depressive symptoms.[70,71] While total seafood consumption was not associated with incidence of depression, Sanchez-Villegas et al found moderate intake of fatty fish was associated with a reduction in depression prevalence. Similarly, moderate intake of lean fish was also associated with a decrease in depressive symptoms. However, the group with the highest intake of fatty fish was not significantly associated with lower frequency of depression.[70]

Smith et al observed a 25% lower risk of depression at follow-up in women who consumed two or more weekly servings of fish compared to women who consumed less than two servings per week. However, no association between fish consumption and depression was found in men.[71]

Gluten Free-Diet

A prospective cohort study found a significant overall improvement in the Hospital Anxiety and Depression Scale (HADS) following a six-week gluten-free diet (GFD) among individuals who have the HLA-DQ2/8 genotype of IBS-D. Eighteen months after the completion of the study, 72% of participants were still on GFD with a continued reduction in depressive symptoms compared to baseline.[72]

Nut Consumption

In an RCT study comparing an almond-low carbohydrate diet (a-LCD) to a low-fat diet (LFD) in T2DM individuals, a-LCD was found to significantly improve depression scores compared to the LFD group. In addition, a significant improvement in short-chain fatty acids (SCFAs)-producing bacteria was observed in the a-LCD group.[73]

In a cross-sectional study, a higher consumption of nuts was associated with a reduction in depressive symptoms.[74]

Soy Consumption

In a cross sectional analysis, soy consumption consisting of 1-3 times per week was associated with the lowest risk of depression, while both the least (less than once per week) and highest (4-7 times per week) frequency of soy food was associated with an increased risk of depression.[75]

Anti-inflammatory & Inflammatory Index Patterns

Two observational studies found an inverse relationship between high adherence to the anti-inflammatory diet (AID) and incidence of depression.[76,77] Shivappa et al found a 20% decreased risk of depression in women who had the highest adherence to AID compared to women with the most pro-inflammatory diet.[76]

Consequently, four observational studies found higher dietary inflammatory index (DII) scores had a positive association with increased incidence of depressive symptoms.[78-81] Adjibade et al found the highest quartile of DII scores was associated with a 15% increase in the risk of depression when compared to the lowest quartile. However, this statistical significance was only observed among women.[78] Phillips et al observed a similar pattern with an inverse relationship between the elevated risk of depressive symptoms and higher DII scores in women only.[79] Contrastingly, one observational study found an increased incidence of depression in men only, although only slightly significant.[81]

Western-style diet & Fast-food

One observational study found a Western-style diet was associated with an increased risk of depression. In addition, a lower diet quality score increased the odds for depressive disorders.[82] The remaining studies demonstrated a strong positive correlation between depressive symptoms and increased frequency of fast food consumption.[83-87]

Adjibabe et al found a 10% increase in the percentage of ultra-processed foods (UPF%) was associated with a 21% increased risk of depressive symptoms. An even higher risk was observed for individuals that consumed a high UPF% in added fats, sauces, and beverages.[83] Sanchez-Villegas et al found a 40% increased risk of depression in the highest quintile of fast-food consumption, while Crawford et al found a positive relationship between depressive symptoms and higher frequency of fast-food intake in women.[84,85]

Results: Micronutrients

Study Characteristics Micronutrient Summary

Table 3 is attached as a PDF document.

Primary Study Findings by Micronutrient

Table 4 is attached as a PDF document.

Vitamin A

Bitarafan et al conducted an RCT measuring the potential impact of vitamin A on fatigue and depression symptoms in a population of multiple sclerosis (MS) patients. The intervention was conducted over twelve months with a higher vitamin A dose of 25,000 IU/day for six months followed by a lesser dose of 10,000 IU/day for an additional six. The intervention group had a significant decrease in depression score, indicating an improvement in depressive symptoms.[88]

Vitamin B

One RCT found a significant improvement in depressive symptoms following a six month intervention of 10mg of folic acid per day.[89] An additional RCT with vitamin B12 and folic acid supplementation over two years found a larger decrease in homocysteine levels in the intervention group, but not a significant difference in depressive scores.[90] Finally, a three-year cohort study looked at the association of intake level of three B vitamins from food and depression. Women in the highest tertile of vitamin B6 intake were found to have a 43% lower risk of depression. Whereas, men with the highest intake of B12 were found to have a reduced risk of depression.[91]

Vitamin D

Three RCT trials found a significant improvement in depressive symptoms with vitamin D supplementation as compared to the placebo group.[92-94] Two additional RCT studies included co-supplementation with a probiotic.[95,96] Raygan et al investigated co-supplementation with Lactocare Zisttakhmir Co in T2DM subjects with CHD and found a significant reduction in Beck score.[95] Ostadmohammadi et al examined the effect of vitamin D plus probiotic (*Lactobacillus acidophilus, Bifidobacterium bifidum, Lactobacillus reuteri and Lactobacillus fermentum*) co-supplementation in women with PCOS. A significant reduction in depression score was found in

the intervention group as compared to placebo.[96] All RCTs implemented a minimum vitamin D intervention of 50,000 IU every 2 weeks.[92-96]

Finally, one RCT comparing individuals with low 25(OH)D levels were assigned to 40,000 IU/week or placebo. Individuals with high serum levels were also used as controls and found to have lower depression scores at baseline as compared to individuals with vitamin D deficiency. Supplementation did not show a significant improvement in depression scores as compared to control subjects.[97]

Multi-Nutrient

Mozaffari-Khosravi et al conducted a twelve-month RCT with a multi-nutrient supplement containing PUFAs, selenium, folic acid, vitamin D3 and calcium. The study compared the rate of onset of major depressive disorder (MDD) in four different groups: multi-nutrient with food therapy, multi without therapy, placebo with food therapy and placebo without. There was no difference in rate of onset between the four groups measured.[98]

Amino Acids

One RCT studied the impact of oral essential amino acid supplementation in nursing home patients. The study did not report a significant difference compared to placebo, but did show an improvement in depressive symptoms in intervention subjects following eight weeks of supplementation.[99]

Magnesium

Rajizadeh et al looked at the impact of magnesium supplementation over eight weeks. Both the intervention (Mg) and placebo groups had an improvement in BDI-II score, but a greater improvement was shown in the intervention group.[100] A cross-sectional analysis of a prospective

cohort of over 2,300 subjects found magnesium intake to be inversely associated with incidence of depression.[101]

Zinc

Zinc supplementation in one RCT found significantly improved BDI scores in the intervention group as compared to controls. Further analysis indicated the significant reduction was found in the subgroup with BDI baseline scores above ten. Additionally, they measured BDNF levels and reported an inverse relationship between BDNF levels and depression severity.[102] Sawda et al looked at zinc with a multivitamin supplement (MV + Zn) compared to multivitamin (MV) only over ten weeks. A significant reduction in depression-dejection score on the POMS was found only in the MV + Zn group.[103]

Results: Supplements, Herbs and Spices

Study Characteristics Supplements, Herbs and Spices Summary

Table 5 is attached as a PDF document.

Primary Study Findings by Supplements, Herbs and Spices

Table 6 is attached as a PDF document.

Probiotics and Prebiotics

One RCT examining the effects of *Bifidobacterium longum* (BL) showed a significantly higher percentage of subjects in the BL group had a decrease in the HADS depression score at 6 weeks compared to the placebo. In addition, the BL group exhibited reduced responses to emotional stimuli in several brain regions.[104] Kazemi et al demonstrated a significant decrease in the BDI score among the probiotic group after 8 weeks compared to the prebiotic and placebo

group.[105] Hadi et al examined the effects of synbiotics in overweight and obese individuals and found a significant decrease in depression scores compared to the placebo group.[106]

Another RCT examining the effects of probiotics in depressive patients with myocardial infarction demonstrated an inverse relationship between BDI scores and probiotic supplementation. In addition, the intervention group experienced a greater reduction in inflammatory markers compared to the placebo.[107] Contrastingly, Romijn et al found no significant difference in depression scores between the intervention (*Lactobacillus helveticus & Bifidobacterium longum*) and placebo group after 1 year.[108]

Two RCTs examined the effects of probiotic and selenium co-supplementation on depressive symptoms.[109,110] One RCT examining T2DM subjects with coronary heart disease found a significant reduction in BDI scores among the intervention group compared to the placebo. A significant reduction in other health markers, such as fasting plasma glucose and insulin resistance were also observed.[109] The second RCT examined women with PCOS and found a significant improvement in BDI scores compared to the placebo.[110]

Omega-3

Six RCTs found an inverse relationship between depressive symptoms and omega-3 fatty acids.[111-117] Park et al observed individuals with MDD for 12-weeks and found omega-3 PUFAs significantly decreased CGI-I scores compared to the placebo. However, other depressive rating scales showed no significant improvement with omega-3 supplementation.[111] Rondanelli et al found a significant improvement in GDS scores among depressed elderly female individuals after 2 months of omega-3 PUFA supplementation.[112]

Another 12-week RCT looked at the effects of omega-3 fatty acids on thalamus glutathione concentration in individuals at risk for MDD. After the 12-weeks, the placebo group experienced

a greater change in glutathione to creatinine ratio compared to the omega-3 fatty acid group. This change was associated with worsening depressive symptoms.[113]

Yang et al conducted a 12-week RCT and found significantly higher depression remission rates in those who were in the eicosapentaenoic (EPA) plus docosahexaenoic (DHA) and EPA only group. There were no significant rates of remission found in the DHA only group.[114] Another 6-month RCT measuring the effects of omega-3 supplementation in elderly individuals found greater improvements in GDS scores among the increased DHA and EPA groups compared to the linoleic acid (LA) group.[116]

Contrastingly, van de Rest et al did not find a significant difference in either the high dose fish oil, low dose fish oil, or placebo group after 26-weeks of intervention with EPA and DHA.[117] Jamilian et al looked at the effects of omega-3 and vitamin E co-supplementation in women with PCOS. After 12-weeks, the intervention group had significant improvements in BDI and depression, anxiety & stress scores compared with the placebo. In addition, the intervention group experienced a down-regulation in pro-inflammatory markers.[115]

Algal Extract

One RCT examining the effects of *Ulva L.L* extract in healthy subjects with anhedonia found a significant reduction in the QID-SR score after 84 days compared to the control with over 90% of individuals reporting improvements in sleep, food behavior, and psychomotor consequences in the intervention group versus the 72.5% reporting improvements in the control group.[118]

CoQ10

Sanoobar et al measured the effects of 500 mg/day of CoQ10 in multiple sclerosis patients with depressive symptoms for 12-weeks and found a significant decrease in the BDI score

compared to the control. A significant reduction in the fatigue severity scale (FSS) was also observed.[119]

Curcumin

In a 16-week RCT, 160 mg/day of curcumin, 2000 mg/day of DHA + EPA, or a combination of both were given to non-depressed overweight or obese individuals. Curcumin was found to reduce mood disturbances and improve vigour, while fish oil had no effect on mental state. However, APOE4 status was found to affect responses to fish oil with non-carriers experiencing a reduction in mood disturbance and increased vigour compared to the control. No additional benefits were observed with the co-supplementation of curcumin and fish oil.[120]

Flavonoid-rich OJ

In an 8-week RCT, young adults with depressive symptoms at baseline consumed either flavonoid-rich orange juice (FR) or flavonoid-low orange juice (FL). The FR group experienced a significant reduction in the CES-D score compared to the FL group. In addition, there was an increase in BDNF levels observed among the FR group, although not significantly different compared to the control. Furthermore, two bacterial species (*Lachnospiraceae and Bifidobacterium*) in the gut significantly increased in the FR group.[121]

Hops

A crossover style RCT measured the effects of *Humulus lupulus L.* plant (hops) on depression, stress, and anxiety in young adults with mild depression. Hops was found to significantly decrease DASS-21 depression, anxiety, and stress scores compared to the placebo.[122]

Jollab drink

An RCT measured the effects of 15 mL of jollab three times daily in depressed individuals with dyspepsia. A significant reduction in BDI scores were found compared to the placebo.[123]

Lemon Balm

An RCT examining the effects of Melissa officinalis (lemon balm) on depression, anxiety, and stress in chronic stable angina patients found a significant reduction in DASS-21 scores compared to the control after an 8-week intervention. In addition, total sleep score significantly improved post lemon balm intervention.[124]

SAMe

A follow-up RCT was performed on individuals with MDD who did not respond to a 6-week intervention with 1600 mg/day SAMe, 10 mg/day escitalopram, or placebo. For the 6-week follow-up doses were doubled. Sakurai et al found a significant reduction in several depression scores including the HDRS-17, CGI-S, and CGI-I scores for all three treatments.[125]

Talbinah food

A 3-week crossover style RCT examined the effects of Talbinah food on depressive symptoms among the elderly in a long term care facility setting. There was a significant reduction in depression, mood disturbances, and stress across all parameters (GDS, DASS, & TMD) for the intervention group. In addition, there was a significant increase in calories, zinc, and magnesium for the intervention group.[126]

Walnuts

A crossover style RCT studied the effect on depressive symptoms by consumption of banana bread with walnuts or banana bread with a placebo. Individuals were randomly assigned to complete eight weeks of intervention or placebo with a six-week washout period before completing the alternative protocol. There was no significant change in mood found in females, although males did exhibit a significant improvement in Total Mood Disturbance score.[127]

Discussion: Dietary Pattern

Dietary Patterns Summary

Mediterranean-style diet

The Mediterranean-style diet has a signature pattern of high intake of colorful vegetables and fruits along with whole grains, fish and olive oil. While there are variations to the dietary pattern, all allow for high intake of plant extracts such polyphenols, which have been shown to possess antioxidant and anti-inflammatory properties.[128] Specifically, anthocyanins responsible for the red to blue or purplish-color roots, vegetables or grains,[129] which are consumed as part of a Med-style diet, have been found to potentially mitigate oxidative stress and systemic inflammation.[130]

Polyphenol & Flavonoid

Dietary polyphenols, found in abundance in foods like berries, nuts, herbs, spices, vegetables, olives, and tea, are plant compounds emerging as therapeutic agents for several neurological conditions due to their adaptogenic and antioxidant properties.[131] The RCT and observational studies reviewed demonstrated an association between decreased depressive symptoms and a high intake of dietary polyphenols.[42-45] Polyphenols have been found to impact depression through the alteration of the gut microbiota by acting as prebiotics, which increase the amount of beneficial bacteria associated with good health.[132,133]

Subsequently, polyphenols such as flavonoids are found to display antidepressant-like activity through the alteration of BDNF levels and the monoaminergic system.[134] In addition, flavonoids exert anti-inflammatory responses through antioxidative mechanisms that alter cytokine expression and oxidative stress.[134]

Low Protein

Two RCTs reviewed found a correlation between increased depressive symptoms and low protein diets.[46,47] Amino acids from animal protein sources such as tryptophan and tyrosine are used by the brain to synthesize neurotransmitters.[135] Low protein in the diet can lead to low levels of neurotransmitters, which is associated with depression. The amino acid tryptophan, found in turkey, chicken, fish, and nuts, is the precursor to serotonin.[136] Serotonin is associated with improving mood and depressive symptoms.[136] However, a diet excessively high in protein is associated with inflammation, thus a moderate intake is recommended for individuals with depressive symptoms.[137]

Chronic Disease Management Dietary Pattern

Depression has been found to be up to two times more likely in individuals with diabetes.[138] Some hypothesize this is due to the similar biological dysfunctional pathways such as inflammation or HPA axis.[138] The two RCTs reviewed within had somewhat conflicting results, although the lack of significance in the second used a diabetes management diet as the control group.[48,49] This control group had improvement in depressive symptoms along with the study using this similar diet as the intervention.[49] Therefore, it can be concluded that a dietary pattern intended to manage diabetes symptoms could also regulate pathways, thereby potentially reducing depressive symptoms.

Healthy Dietary Pattern

The healthy dietary pattern is similar to a Mediterranean diet with an increase in vegetables, fruit, lean protein, fish, nuts, seeds and olive oil along with reduction in processed and sugary foods. The RCT reviewed within showed a significant decrease in depressive symptoms in a short 3-week intervention.[50] Change in the microbiota make-up of an individual can occur rather

rapidly. One study that compared a plant-based diet to an animal-based diet showed significant change to the microbiome taxa after only five days of consumption.[139] Interestingly, it was also found that the animal-based diet had a larger impact on the microbiota in the short timeframe,[139] which could also indicate that the consumption of a less healthy dietary pattern, lower in plant-based foods, may negatively impact an individual quickly. The quick change in microbiome can also indicate that intake of a healthy dietary pattern may prove a better prevention or treatment for individuals' depressive symptoms compared to antidepressant medications, which can take weeks or longer to impact symptoms.[29]

Healthier Dietary Pattern

One healthier dietary pattern was a reduction in red meat consumption to less than five times per week.[62] In an RCT, a reduction in inflammatory markers was found when soy was replaced for red meat consumption in a DASH-style dietary pattern.[140] Another healthier diet was focused on weight loss, which also included counseling on dietary factors that would improve microbiome.[63] An increase in fiber intake was highlighted, which has been found to be associated with brain health including improvement in psychological disorders.[63,141] Intervention studies have shown increasing intake of fiber rich foods such as fruits, vegetables, and whole grains has the potential to reduce the severity of depressive symptoms.[142]

Finally, a Japanese-style healthy dietary pattern included mushrooms as a component.[64] Mushrooms have a unique nutrition profile with B vitamins, selenium and zinc included.[143] Additionally, mushrooms are the only plant source of vitamin D, and levels can be impacted by growing conditions or utilization of UV lights.[143] Vitamin D deficiency can play a role in depression risk,[144] and consumption of enriched mushrooms could be beneficial.

Plant-Based Dietary Pattern

A plant-based dietary pattern has been studied for many chronic conditions. In a large cohort of over 65,000 participants, vegans were found to have the highest intake of vitamin B1, folate, vitamin C and vitamin E, magnesium and iron.[145] Folate, which is higher in plant foods versus animal products, is necessary for monoamine synthesis.[146] And whether due to the naturally high levels of polyphenols, antioxidants or fiber in a plant-based diet, a vegan diet has been associated with an increase in beneficial microbiota and microbiome diversity.[147] Another highlighted component of a plant-based diet is the potential anti-inflammatory factor. In an RCT, a vegan diet was found to significantly reduce the CRP levels as compared to the American Heart Association (AHA) diet, specifically designed to be anti-inflammatory.[148]

Glycemic Index

The studies reviewed found high glycemic index (GI) foods or a high glycemic load (HGL) dietary pattern to be associated with an increased risk of depression.[68,69] While a high glycemic load has been associated with an increase in pro-inflammatory markers,[149] high GI foods have also been correlated with increased cortisol levels.[24]

Fish Consumption

The observational studies reviewed found an association between moderate fish consumption and a reduction in depressive symptoms.[70,71] Fish contains a high level of omega-3 fatty acids and tyrosine, which are both beneficial for brain health.[150] Tyrosine is the precursor to several neurotransmitters including dopamine, epinephrine, and norepinephrine.[151] Omega-3 fatty acids contain eicosanoids, which play a role in fighting inflammation and regulating the immune system. Depression has often been associated with an increase in proinflammatory cytokine production. However, a high consumption of omega-3 containing fish can potentially downregulate cytokine production through the immunoregulatory eicosanoids.[152]

Gluten-Free Diet

While only one cohort study examined the correlation of gluten and depressive symptoms, a significant improvement in depressive symptoms was found in those that consumed a gluten-free diet.[72] Gliadin, a protein found in wheat, has been shown to induce zonulin release, which can lead to a temporary increase in intestinal permeability.[153] Even though the expression of permeability is not as great in non-celiac disease individuals, chronic exposure to gliadin was shown to downregulate tight junction gene expression regardless of genetic expression.[153] In patients with MDD, increased zonulin-mediated permeability has been found along with increased pro-inflammatory expression.[154]

Nut Consumption

Nuts contain many nutrients that are found to be beneficial for reducing risk of depression. Although selenium levels in food can vary depending on region and soil quality, higher protein foods, such as nuts, can be a rich dietary source of selenium.[155] Selenium has been shown to play a role in risk of depression potentially via the attenuation of inflammation and also modulation of oxidative pathways and neurotransmitters.[156] Additionally, supplementation during pregnancy has been found to significantly reduce risk of postpartum depression.[157]

Soy Consumption

While serine is a non-essential amino acid, we can also obtain it from certain foods, such as soy.[158] Serine has been shown to be involved in the NMDA receptor function,[159] and studies have found an indication that low levels of serine may correlate with severity of depression.[160] Additionally, soy is also a good plant-based tryptophan source.[161] As discussed above, high levels of protein intake can be associated with increased systemic inflammation, so moderate intake of plant-based tryptophan can be beneficial for monoamine synthesis. Finally, a reduction in

inflammation markers following consumption of a diet rich in soy after eight weeks has been observed.[140]

Anti-inflammatory and Inflammatory Index Patterns

In similar findings as the observational studies reviewed, a recent systematic review found a higher DII score to be correlated with an elevated risk of depression and increased concentration of circulating proinflammatory markers.[162] Inflammatory biomarkers can cross the blood-brain barrier, therefore potentially disrupting monoamine synthesis, neuronal plasticity and other neuronal regulation.[28] Interestingly, the higher risk of depression remained even when inflammation markers were controlled for in comparison,[28] which could indicate the potential impact of diet alone in short-term intake. In the observational studies reviewed, two found a significant association between dietary inflammatory index in women only.[76,77] The systematic review did not indicate a gender difference, but did suggest poor nutritional status, such as obesity and lower energy intake, may contribute to inflammatory potential of diet consumed.[162]

Western-style diet & Fast-food

All studies reviewed found an association between higher depression scores and increased consumption of processed and fast-foods often linked to the Western-style diet.[82-87] The Western diet is characterized by high-fat, high-sugar, pre-packaged, processed foods that lead to chronic inflammation. Immune cells located in the gut become dysregulated by a diet high in sugar and fat, making the gut more prone to inflammation.[163] Chronic inflammation of the gut results in inflammatory bowel diseases (IBD), which are associated with a higher risk of depression.[164]

Consequently, Western-style diets are also low in dietary fiber. Low-fiber diets are also associated with depression because they often lead to an increase of inflammatory biomarkers such as IL-6 and IL-8.[165] Contrastingly, a diet high in fiber can decrease inflammation in the body by

modifying gut permeability and inducing microbiota changes that can lead to an increased production of neurotransmitters.[166]

Discussion: Micronutrients

Discussion: Micronutrient Summary

Vitamin A

Oxidative stress can impact neurotransmitter synthesis and function. Vitamin A has been shown to be an effective antioxidant.[167] It also plays a role in immune competence, is important for the production of regulatory T helper cells and interacts synergistically with other nutrients important in risk of depression such as zinc.[168,169]

Vitamin B

The studies reviewed within support the essential intake of B vitamins.[89-91] Folate is necessary for the modulation of monoamine synthesis.[146] It has also been indicated that folate levels may be dose-dependent meaning depression severity may increase with higher levels of deficiency.[170] Additionally, low levels of vitamin B6 have been found to be associated with increased risk of depression.[171] B6 is a cofactor for the production of serotonin,[28] therefore deficiency may impact monoamine levels. Specifically, deficiency levels have been correlated with severity of disease.[172]

Deficiency in B vitamins reduces the modulation of oxidative stress caused by elevated homocysteine levels.[173] With an increase in oxidative species, brain function can be altered including decrease in neurotransmitters.

Vitamin D

Individuals with higher levels of vitamin D were found to have lower depression scores compared to individuals with a vitamin D deficiency at baseline.[92-96] Studies have shown several vitamin D receptors are present in the brain and control neurotrophic factors that may initiate neuroprotective benefits.[174] In addition, vitamin D influences the immune system by downregulating proinflammatory responses associated with depression while promoting anti-inflammatory pathways.[175] Furthermore, vitamin D is associated with the formation of serotonin by promoting the expression of serotonin receptor, TPH2.[176]

Multi-Nutrient

While the nutrients contained in this supplement, omega-3, selenium, folic acid, vitamin D, have all been found in some studies to potentially reduce risk of depression, the RCT reviewed within did not find a significant reduction in risk of depression.[98] As reported by the researchers, the onset of MDD was lower than expected across all groups, thereby reducing the power to detect significant change.[98] Additionally, there was no baseline serum analysis or throughout, so it is unknown if there were deficiencies prior or if there were differences in serum levels between the groups following supplementation.[98]

Amino Acids

In the observational study reviewed, amino acid supplementation was shown to improve depressive symptoms after eight weeks of intervention.[99] Amino acids are often regarded as key nutrients in the prevention and treatment of depression because they are essential for the synthesis of several neurotransmitters.[177] The amino acid phenylalanine is necessary to produce tyrosine, the precursor to dopamine and norepinephrine.[178] On the other hand, depletion of tryptophan, the precursor to serotonin, is associated with both depressive relapses in those with depression and increased low mood in those who are at high risk for depression.[179] Furthermore, the amino acid

methionine is also necessary to produce SAMe. Lower levels of SAMe have been found in depressed individuals.[180]

Magnesium

The evidence is limited on magnesium supplementation although intake levels have been inversely correlated with depression.[100,101] A recent literature review concluded the same findings and highlighted the potential mechanism of deficiency to be related to HPA axis dysregulation and increased systemic inflammatory response.[156]

Zinc

Limited trials have been conducted, but both RCTs included within reported an improvement in depression scores although one combined zinc supplement with a multivitamin.[102,103] Additionally, a recent review concluded there is strong support in the literature for the increased risk of depression with zinc deficiency partially due to its mood-enhancing effects.[156] The possible mechanisms of deficiency may be increased cortisol levels and decreased neuronal plasticity.[156]

Discussion: Supplements, Herbs and Spices

Supplements, Herbs and Spices Summary

Probiotics and Prebiotics

Probiotic, prebiotic, and synbiotic supplementation were all associated with significant improvements in depressive symptoms compared to the control groups.[104-110] While depression severity and bacterial strains varied significantly, probiotic supplementation seems to influence depressive symptoms through the regulation of the inflammatory response.[104,105,107,108] Depressed individuals often have high levels of inflammation, which can lead to increased intestinal

permeability. Probiotics promote the quantity and diversity of beneficial bacteria which may improve intestinal endothelial lining and reduce the amount of toxins entering the bloodstream, in turn improving inflammation.[181]

Consequently, probiotic-induced changes in the microbiome are found to greatly influence serotonin transmission in the CNS and PNS.[182] Probiotics may also improve the availability of serotonin through the augmented production of circulating tryptophan as probiotic supplements have been shown to affect tryptophan metabolism.[183]

Omega-3

Omega-3 fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) found in fatty fish and fish oil help regulate the inflammatory response and have shown to be protective against mood disorders such as depression.[19,184] The evidence reviewed found improvement in depressive symptoms with EPA and DHA supplementation with only one trial showing insignificant difference in subjects compared to placebo.[111-117] Cohort studies have found an inverse relationship of low n-3 PUFA levels and increased levels of pro-inflammatory markers such as IL-6, TNF-alpha and CRP.[185] As discussed earlier, increased levels of systemic inflammation have been positively correlated with elevated depressive symptoms. Additionally, Thesing et al found low n-3 PUFA levels were associated with high evening cortisol.[185] The finding of high cortisol in the evening could signal HPA axis dysfunction, indicating the potential complementary treatment with omega-3.

Algal Extract

Algae has been studied for its potential health benefit as it is a rich source of polysaccharides and flavonoids.[186] The prebiotic nature of these compounds can play a role in gut

endothelial health and abundance of healthy microbiota. As mentioned throughout, these factors have been shown to contribute to reduced inflammation.

CoQ10

In the RCT reviewed, CoQ10 supplementation was associated with a significant reduction in depression scores.[119] Although research is limited, lower levels of plasma CoQ10 are often seen in depressed individuals.[187] CoQ10 is an antioxidant that has strong anti-inflammatory effects. While the body produces it naturally, lower levels caused by aging, disease, or medications can increase oxidative damage inducing an inflammatory response in the body.[188]

Curcumin

The study within was a secondary analysis of an RCT in order to examine the impact of curcumin or synergistic impact with fish oil.[120] The data is limited from this study, but curcumin has been studied by many to determine the antioxidant and anti-inflammatory potential.[189] One challenge is the bioavailability and instability of some formulations,[189] however a review of plant polyphenols, including curcumin, suggests that even a moderate use of low-dose polyphenols daily can have neuroprotective benefit via upregulated antioxidant cascades reducing inflammation.[190] Again, this conclusion highlights the benefit of a diet rich in polyphenols.

Flavonoid-rich OJ

In the RCT reviewed, FR orange juice was associated with a significant reduction in depression scores compared to the FL group indicating flavonoids may have an antidepressant effect.[121] The flavonoid naringenin, found in citrus fruits, exhibits neuroprotective qualities and inhibits monoamine oxidase (MAO) activity associated with decreased monoamine levels.[134] Thus, a high intake of naringenin may result in the reduction of depressive symptoms by maintaining balanced monoamine levels through the inhibition of MAO activity.[191]

Hops

The RCT reviewed found an association between decreased depressive symptoms and hops.[122] While evidence is limited, hops may reduce depressive symptoms by interacting with serotonin receptors, exerting antidepressant-like effects.[192]

Jollab drink

Jollab is a Persian drink that contains saffron.[123] A recent meta-analysis by Toth et al found saffron to significantly impact severity of depression.[193] Saffron is rich in carotenoids and flavonoids, contributing to its use as an antioxidant.[194]

Lemon Balm

Lemon balm is rich in antioxidant flavonols and flavonoids. As discussed above, flavonoids may have an antioxidant effect, and may also improve insulin resistance. Asadi et al found an improvement in HbA1c and *B*-cell function, and also a reduction in inflammation.[195] Antioxidant and anti-inflammatory effects of lemon balm may provide benefit in multiple pathways related to risk of depression.

SAMe

The RCT reviewed found a significant reduction in depression scores after SAMe doses were doubled in individuals with MDD, indicating high levels of SAMe may be needed in those with severe depression.[125] While SAMe is produced naturally in the body, low levels are often seen in those with depression. While research is limited, SAMe is found to increase the levels of serotonin, norepinephrine, and dopamine.[180]

Talbinah food

Talbinah is a high-carbohydrate food component mixed with water for consumption.[126] As suggested by Wurtman et al, high carbohydrate intake can positively influence the ratio of

tryptophan in the blood for uptake by the brain.[196] Talbinah has a high ratio of tryptophan, and as previously discussed is important for the production of monoamines. Additionally, Talbinah has magnesium and zinc, which have both been implicated in association with depression.[126] The study was small with only 36 elderly subjects, but depressive symptoms were significantly decreased.[126]

Walnuts

Although the RCT reviewed within did not show significant reduction in depressive symptoms, RCT studies have shown significant changes in microbiome during a walnut-rich diet.[127,197] In a crossover style RCT, participants consumed 43 grams of walnuts during an 8-week intervention period and also an 8-week period of no nut consumption. Fecal analysis showed significantly more probiotic-type species and butyric-acid producing species.[197]

Conclusion

Depression negatively impacts overall health and well-being making the rising rates of prevalence a significant global issue. The use of antidepressants and continued rates of relapse demonstrate the need for alternative treatments. Additionally, the increased global consumption of a Western-style diet and decreased overall diet quality found during the pandemic are currently contributing to the steadily rising rates of depression. These rates will likely continue to increase following this traumatic event indicating the need for a significant shift in dietary intake among the global population. Proper nutrition has a significant impact on overall health and reduced risk of disease, likely from the potential to modulate pathophysiological factors in depression. Therefore, this review examined the evidence regarding nutrition intervention studies related to potential treatment and prevention of depression. The Mediterranean-style and anti-inflammatory dietary patterns, in addition to omega-3 supplementation were associated with the greatest

improvements by potentially mitigating oxidative stress and systemic inflammation associated with depression. Supplementation of certain nutrients including amino acids, B vitamins, vitamin D, zinc, and magnesium were associated with a decrease in depressive symptoms potentially due to their involvement in monoamine neurotransmitter synthesis and overall neuroprotective benefits. Additionally, dietary intake of polyphenols, flavonoids, fiber, probiotics, low glycemic index foods and elimination of gluten were correlated with reduced depressive symptoms likely due to the improved tight junctions of the endothelial lining, regulation of the HPA axis, and the modification of the gut microbiota composition. Based on the evidence, it can be concluded that a targeted nutrition protocol can be proposed for future study.

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Proposed Nutrition Protocol for the Prevention and Treatment of Depression

Introduction

Rates of depression have been rising over the last decades and an even greater increase has been found since the start of the COVID-19 pandemic.[1,2] An unhealthy diet consisting of ultra-processed foods, high intake of unhealthy fats, red meat and sweets have been found to be

associated with the increase in prevalence.[1] Additionally, antidepressants have been found to be ineffective in many with almost half not experiencing elimination or improvement in depressive symptoms.[3] Nutrition is often overlooked for the prevention and treatment of depression while numerous studies have associated nutrition with a significant reduction in symptoms. A well-balanced diet consisting of dark leafy greens, vegetables, fruit, whole grains, and healthy fats can reduce an individual's susceptibility to depression. The factors that can be influenced by a well-balanced diet include:

- The health of the gut microbiome and the bidirectional communication of the gut-brain axis[4-7]
- Level of systemic inflammation[8-14]
- The essential nutrients for monoamine neurotransmitter synthesis[15-17]
- Regulation of the HPA axis[18-21]

Risk Factors

- Genetics-family history[22]
- Gender-females are more likely to be depressed[23]
- Overweight or obesity[23]
- Anxiety[22]
- Diet[22]
- Comorbidity/Chronic Illness[23]
- Poor Sleep Hygiene[22]
- Sedentary lifestyle[22]

Nutrients for Mood and Brain Health

The nutrients below are considered essential nutrients related to depression.

Nutrient	Evidence-based Association to Depression Risk
B Vitamins	B vitamins are necessary for the modulation of monoamine neurotransmitter synthesis[24]; Deficiency correlated with severity and inflammation.[25-27]
Vitamin D	Several D brain receptors may initiate neuroprotective benefits and expression of serotonin receptor, TPH2[28-29]; D influences the immune system by downregulating proinflammatory responses.[30]

Magnesium	Deficiency may be related to HPA axis dysregulation and increased systemic inflammatory response.[31]
Omega-3	Helps regulate the inflammatory response[14]; Deficiency associated with high evening cortisol and increased levels of pro-inflammatory markers,[32] indicating potential HPA axis dysfunction with low levels.
Selenium	Attenuates inflammation and modulation of oxidative pathways and neurotransmitters.[33]
Zinc	Mood-enhancing effects; Deficiency associated with increased cortisol levels and decreased neuronal plasticity.[33]

Dietary Pattern

Below is a summary of the evidence for positive and negative dietary pattern factors related to risk of depression.

Dietary Pattern	**Evidence-based Association to Depression Risk**
Mediterranean, Anti-inflammatory Diet & Alternative Healthy Eating Index	High intake of plant extracts possess antioxidant and anti-inflammatory properties.[34] Anthocyanins potentially mitigate oxidative stress and systemic inflammation[35-36]; Polyphenols impact through alteration of the gut microbiota[37-38]; Flavonoids exert anti-inflammatory responses altering cytokine expression and oxidative stress[39]; Increase in fiber positively associated with brain health and reduction in severity of symptoms[40-42]; Higher DII score correlated with an elevated risk of depression and increased proinflammatory markers.[43]
Dietary Pattern	**Evidence-based Association to Depression Risk**

Gluten-Free Diet	Gliadin, shown to induce zonulin release, can lead to a temporary increase in intestinal permeability. While greater in celiac individuals, even chronic exposure to gliadin was shown to downregulate tight junction gene expression. In patients with MDD, increased zonulin-mediated permeability has been found along with increased pro-inflammatory expression.[44]
Nut Consumption	Nuts contain many nutrients that are found to be beneficial for reducing risk of depression, such as selenium. Selenium has been shown to play a role in risk of depression potentially via the attenuation of inflammation and also modulation of oxidative pathways and neurotransmitters.[45-46]
Western-style Diet & Fast-food; High Glycemic Index	Immune cells in the gut become dysregulated with a processed diet, making the gut prone to inflammation.[47] Chronic inflammation of the gut results in inflammatory bowel diseases, associated with a higher risk of depression.[48] Low-fiber diets, such as the Western diet often lead to an increase in inflammatory biomarkers.[49] Additionally, high GI foods have also been correlated with increased cortisol levels.[20,50]

Microbiome Health

A diverse and dense microbiome has been found to associated with a decreased risk of disease, whereas a less diverse or disrupted balance, also known as dysbiosis, is found to be associated with an increased risk of disease including depression.[4-6] The bidirectional communication between our enteric nervous system and central nervous system via the vagus nerve is known as the gut brain axis (GBA).[7] Disruption to the GBA can influence changes in gut microbiota composition, while modification of the microbiome can induce depressive-like behavior.

- Prebiotics and probiotics
    - Taking prebiotics and probiotics together is known as microbiome therapy. Prebiotics can help strengthen probiotic bacteria, thus taking prebiotics and probiotics in combination can potentially make probiotics more effective.[51]
- Fiber
    - Fiber is an essential component of the gut microbiome because it is fermented by the bacteria in the gut creating an abundance of short-chain fatty acids (SCFAs), which are thought to be the primary mechanism of metabolic interactions between the microbiota and host.[13]
- Variety of foods

- The types of foods one consumes can have a significant impact on the gut microbiota. Eating a diverse range of whole and plant-based foods can lead to a more diverse microbiome compared to a low intake.

Proposed Protocol

This proposed protocol is intended for the prevention of depression or as a complementary treatment for mild to moderate depression. It is not recommended to replace antidepressant medications unless specified by a physician.

Nutrition Recommendations

Recommendations for the proposed protocol focus on the genetic, epigenetic, and metabolic mechanisms associated with oxidative stress/inflammation, the gut-brain axis, and nutrient deficiencies associated with depression.

- Goals of the proposed protocol that apply to individuals who are at risk or diagnosed with mild to moderate depression
  - Increase whole food consumption of fruits and vegetables and avoid ultra-processed foods and added sugars
  - Achieve and maintain optimal levels of essential nutrients for brain health such as, B vitamins, omega-3 fatty acids, zinc, selenium, vitamin D, and magnesium
  - Restore gut microbiome balance and digestion, absorption, and elimination functions by increasing fiber intake, consuming fermented foods, supplementing with probiotics and digestive enzymes, and limiting gluten
  - Increase nutrient antioxidants, such as vitamin C, vitamin E, carotenoids, polyphenols, and flavonoids to combat free radical production, oxidative stress, and inflammation

The proposed protocol below highlights servings daily or weekly by category. Each category has an intended serving recommendation along with top nutrient foods within each category. These foods are not the only recommendations, but shown for example as the top sources of essential depression nutrients or food components such as fiber. The column on the right hand side shows the nutrient or dietary component that was used to rank the foods. If an individual does not consume a food or foods listed, additional nutrient-dense foods by category may be recommended.

Dietary Component	Servings	Nutrient Ranking
Vegetables	5 or more servings daily	
Group A - Dark Greens	2 or more servings	B Vitamins, Polyphenols & Flavonoids
Group B - B Vitamin	2 or more servings	B Vitamins
Fruit	3 or more servings daily	
Group A- Berries	2 or more servings	B Vitamins, Antioxidants, Flavonoids
Group B- B Vitamin	1 or more servings	B Vitamins
Legumes	2 servings daily	Fiber, Plant-based tryptophan
chickpeas	Soy 1-3 times weekly	
navy beans		
lentils		
Whole Grains	2 servings daily	Fiber
quinoa		
oats		
gluten-free sprouted bread		
Fish	3 or more servings per week (6 oz)	Omega-3
Fatty Fish		
Nuts	1 serving daily (1 oz)	Se, Mg, Zn
brazil nuts		
cashews		
almonds		
walnuts		
Seeds	1 serving daily (1 oz)	Se, Mg, Zn
pumpkin / hemp		
sunflower		
flax / chia		
Turkey, Chicken	up to 1 serving daily (4oz)	Tryptophan, B12
Red Meat	up to 1 serving per week (3 oz)	B12, Tryptophan
Dairy	up to 1 serving daily	B12, Vitamin D, Tryptophan
eggs		
yogurt		
Herbs & Spices	Frequent use daily	Anti-inflammatory, Prebiotic
cinnamon, ginger, tumeric,		
garlic, lemon balm, rosemary,		
saffron, thyme, nutmeg		
Fermented Foods	3 servings weekly	pro- & prebiotics
kimchi, miso, tempeh		
sauerkraut, pickled vegetables		
Sweets	1-2 squares daily	Antioxidants
dark chocolate-72% or higher		

Vegetable and Fruit Groups

In addition, vegetable and fruit categories are each divided into two groups as listed below. For vegetables, Group A dark greens are ranked by most nutrient dense per 1 cup serving and Group B is ranked by highest quantity of vitamins B6 and B9. Additionally, the recommended 3 servings for fruits includes 2 or more servings from group A and 2 or more servings from Group B to ensure adequate amounts of B vitamins, polyphenols, and flavonoids.

Vegetables Group A Dark Greens (2+ servings daily)
watercress
spinach
kale
mustard greens
swiss Chard
dandelion greens
lettuces
bok choy
spirulina
sea vegetables
brussel sprouts
broccoli

Vegetables Group B Vit B6 + B9 Ranking (2+ servings daily)
avocado
green peas
bell peppers
artichokes
beets
corn
turnip greens
butternut squash
asparagus
cauliflower
sweet potato
carrots
mushrooms
tomatoes

Fruits Group A B6 + B9 Ranking (2+ servings daily)
boysenberry
elderberry
blackberry
strawberry
raspberry
blueberry

Fruits Group B B6 + B9 Ranking (1+ serving daily)
bananas
mango
papaya
pomegranate
pineapple
oranges

Additional Intake

Protein

- Recommend minimum of .8g/kg
- Regularly consume protein sources higher in tryptophan such as turkey, chicken, tofu, or fish

Fiber

- Recommend a minimum of 38g of fiber daily for women and men

Fluid

- Adequate fluid intake is important for proper digestion and overall health
- A diet higher in fiber intake requires an increased level of fluid
- At least 10 cups or 80 fl oz of water daily, more as needed based on activity level, temperature, pregnancy or breastfeeding
- 1-3 cups of coffee or tea daily
- Limited fruit juice, soda or other sweetened beverages
- Alcoholic beverages - limit to one per day for women or two per day for men
- Consuming the recommended servings of fruits and vegetables also provides added fluid intake

Fats

- Consume unsaturated fats such as olive oil, flax, walnut, and avocado
- Avoid saturated fats such as butter

Added Sugar and Processed Foods

- Limit added sugars to 10g or less per day
- Avoid processed and pre-packaged foods
- Avoid artificial sweeteners
- Recommend natural sweeteners such as honey, maple syrup, and dates

Sample Menu

The table below shows a sample weekly menu that includes meals consisting of foods from the proposed dietary protocol. The meals were created using foods containing key nutrients that play a role in optimal brain functioning. Each day includes the recommended daily servings for each category as well as the weekly recommended servings for each essential depression nutrient.

The sample menu provides examples for a complete weekly menu. Goals can be set to include a certain number of meals each week gradually increasing to consuming a weekly menu that includes all the recommended daily and weekly servings by category.

	Breakfast	AM Snack	Lunch	PM Snack	Dinner

Mon	Oatmeal w/ plant-based milk, berries and a banana	Green pea hummus w/ bell pepper & carrot sticks	Greens & grains bowl w/ tofu, pickled beets, veggies and sunflower seeds	Brazil nuts and berries	Salmon w/ mango salsa and quinoa salad
Tues	GF whole grain wrap w/ spinach and veggies and an orange	Yogurt with chia seeds and berries	Salad w/ lentil taco "meat" and veggies	Nuts and red pepper hummus	GF pasta w/ marinara & turkey meatballs, berries w/ balsamic
Wed	Avocado toast w/ pumpkin seeds and berries	Roasted chickpeas and banana	Chickpea and tofu curry w/ wilted greens over brown rice	Berry smoothie w/ plant-based milk and nuts	GF veggie pizza, salad
Thurs	Oat bars w/ hemp seeds, berries and banana	Veggie & spinach with red pepper hummus roll ups	Baked sweet potato w/ cheese & veggies and kale pomegranate salad	Berries and nuts	Salmon w/ roasted beet salad and rice & beans
Fri	Peanut butter and strawberry GF toast w/ a banana	1 hard-boiled egg and nuts	GF veggie panini w/ sauerkraut and salad w/ berries	Guacamole w/ pumpkins seeds and GF chips	Vegan shepards pie w/ lentil & sweet potato, walnut salad
Sat	Hashbrown, mushroom, asparagus, tomato scrambled tofu and beans	Yogurt w/ chia seeds and berries	Bean chili w/ almond salad	Strawberry & orange smoothie w/ plant-based milk and nuts	Chicken fajitas w/ veggies and greens
Sun	GF protein pancakes w/ berries	Pineapple and nuts	Veggie bean burger w/ roasted squash and quinoa salad w/ sunflower seeds	Whole grain GF bread w/ berry mash and flax seeds	Greens & grains bowl w/ miso salmon, navy beans and veggies

It is recommended for the essential depression nutrients to be consumed via food where possible. It is suggested to have patients track daily intake on Cronometer, or similar application. Daily intake should be monitored weekly and adjustments to intake or supplements made as needed. Following complete nutrition protocol adherence, intake should be monitored monthly until serum levels are within range. Once serum levels are in range, intake should be monitored every three to six months.

The recommended daily intake and reference ranges for serum levels of the essential depression nutrients are shown below. Due to the biochemical individuality of each person, supplementation for these nutrients may be recommended if needed under the supervision of a registered dietitian, certified nutritionist or physician.

Nutrient	Recommend Intake
Vitamin B3	females:14 mg/day males: 16 mg/day
Vitamin B6	1.3 mg/day for adults
Vitamin B9	400 mcg/day for adults
Vitamin B12	1.8 mcg/day for adults
Vitamin D	400-800 IU/day for adults
Magnesium	females: 310-320 mg/day males: 400-420 mg/day
Omega-3	females: 1.1 g/day males: 1.6 g/day
Selenium	55 mcg/day for adults
Zinc	females: 8 mg/day males: 11 mg/day

Additional Protocol Factors

Individualizing

- Diet History
    - Obtain a complete history to individualize goals, preferences and determine potential nutrient deficiencies
- Risk factors
    - Determine list of potential risk factors and adjustments that can be made to any modifiable factors
- Compliance
    - Develop list of preferred foods and preparations such as baked or steamed
    - Set manageable goals
- Higher protein intake may be needed for older individuals
- Special dietary patterns (vegan, vegetarian, religious dietary restrictions, etc)

    - If not consuming enough dairy (milk, eggs, cheese) or meat, supplement B12 or consume nutritional yeast

Weight Management

- If the individual is overweight or obese, caloric intake and exercise should be managed to reduce weight to a normal BMI
- The proposed protocol is not set for a specific caloric intake but reduced caloric intake should follow general category breakdown to obtain necessary level of essential depression nutrients
    - If caloric intake is reduced, supplementation of essential depression nutrients should be monitored

Other Supplements

- CoQ10
- Curcumin
- 5-HTP
- St. John's Wort
- Tryptophan
- Ginseng

Exercise

- Minimum of 3 exercise sessions weekly
    - 30+ minutes at 70-85% of maximum heart rate
- In addition to exercise, move frequently throughout the day
    - Aim to move at least once for a minimum of five minutes every hour during the day where possible

Sleep Hygiene

- Minimum of 7-8 hours of sleep nightly
- Set a routine and consistent schedule
- Limit light in the room / area
- Turn off electronic devices when possible
- Get daylight exposure
- Limit caffeine consumption in the evening

Mindfulness

- Reduce Stress
    - Focus on breathing or other routine to lower anxiety or stress
    - Delegate or say no to commitments as needed
- Yoga

- Meditation
    - Practice daily
- Practice mindful eating - particularly during stress
    - Regularly scheduled meals / snacks as possible
    - Dine with others as possible
        - If eating alone, avoid social media or internet scrolling
    - Stock pantry with healthy choices
    - Set a weekly menu

Self-care

- Take time for yourself daily
- Journal thoughts and feelings daily or as possible

Antidepressant medication

- The information contained within is not intended to replace medication. Any modifications to dosage level or or discontinuation of use should be discussed with the individual's doctor. While this protocol is intended to provide the nutrition needed for optimal brain health and mood, it should be followed along with guidance of the individual's doctor if being actively treated for depressive symptoms.

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FOR PRESENTATION

- **Slide 1-Title**
  - Good afternoon, my name is Camilla and Nicole. Today we will be presenting A Systematic Review to Propose an Evidence-based Nutrition Protocol in Depression.

- **Slide 2-Content Overview**
  - During this presentation the following topics will be discussed, including: Background for the project, the prevalence & pathophysiologies of depression, evidence from the systematic review, our American Nutrition Association poster experience, and the proposed nutrition protocol.

- **Slide 3 - Background**
  - We chose depression as a topic for our project after doing an integrative approach for another course during the winter semester. While completing our previous presentation together, new data was published indicating a significant increase in depression prevalence since the start of the COVID-19 pandemic and therefore decided to research this topic even further.
  - Experiential - As part of our class we each completed several hours of virtual activities that emphasized the importance of nutrition for overall brain health including mental illness. We listened to several health professionals including nutritional psychiatrists, medical doctors, professors, and functional nutritionists that linked the nutritional role that diet can play in depression.
  - Since proper nutrition can play a major role in reducing the risk of depression, a systematic review was performed to determine if there is currently enough data to create an evidence-based nutrition protocol for the prevention or treatment of mild to moderate depression.

- **Slide 4-Quote**
  - While doing the integrative approach project, we found this quote and wanted to share it again as it is very relevant to what we are discovering today and this was written almost 150 years ago.
  - The quote states “Depression is due to an abnormal condition of the psychic organ dependent upon a disturbance of nutrition”- by Richard von Krafft-Ebing from Textbook of Psychiatry

- **Slide 5-Depression background/facts**
  - Depression currently affects more than 264 million people globally making it one of the top three global burdens of disease
  - As of 2020, it is the leading cause of disability worldwide and the second cause of disability in the US for individuals under the age of 60
  - Rates have been rising steadily over the last decades partially due to the increased intake of ultra-processed foods along with high intake of unhealthy fats, red meat and sweets

★ **Slide 6-Covid**

- Now, an even greater increase in rates of depression are being observed from the social isolation, personal loss, and socioeconomic instability brought on by the COVID-19 pandemic
- Early in the pandemic in April of 2020, rates of depressive symptoms had increased to 27.8%, in comparison to the 8.5% prior to the pandemic.[5] And then, as of December 2020, 42% percent of individuals surveyed by the US Census Bureau reported symptoms of depression compared to 11% in January 2019.[6]
- The chart on the right hand side shows not only the continual increase of depression prevalence year over year but also highlights the exponential increase over the last two years.
- The rapid increase in numbers indicates a need to improve the way depression is currently being approached.

★ **Slide 7-Pathos Intro**

- Many factors play a role in the development of depression. Here are the four main pathophysiologies of depression and how diet impacts each. The factors that will be discussed include: inflammation, the HPA and Gut-brain axis, and the monoamine neurotransmitter hypothesis.

★ **Slide 8- Pathos: Inflammation**

- The first factor connected to depression is systemic inflammation.
- Overweight and obesity are considered a risk factor for depression because the systemic inflammation often associated affects the parts of the brain that help regulate mood and emotions
- Data from a large sample study found that obesity was associated with an increased risk of depression.[10] Over 1 in 3 people worldwide are considered overweight or obese putting a large portion of the population at potential risk
- Additionally, a high ratio of omega-6 to omega-3 is also often reported in adults with depression.[19] Western diets are characterized by a ratio of omega-6 to omega-3 of approximately 15:1, indicating a low intake of omega-3 and an excessive intake of omega-6
- An unhealthy dietary pattern has been correlated with low-grade chronic inflammation as evidenced by an increase in pro-inflammatory markers like IL-6, IL-2, and CRP.[11]
- Contrastingly, a healthy dietary pattern is associated with increased levels of brain-derived neurotrophic factor (BDNF) and anti-inflammatory markers.[12] BDNF is a key molecule involved in neuroplasticity, and decreased levels have been associated with depression.[13]

★ **Slide 9 - Pathos: HPA axis**

- A second factor connected to depression involves the HPA-axis.
- The HPA axis is a negative feedback loop involving the hypothalamus, pituitary gland, and adrenal glands. The dysregulation of this axis can be caused by the continuous output of cortisol, which can be stimulated by chronic stress, processed foods, and sugar.[23] Studies have found that high glycemic diets are associated with an increase in cortisol levels.[24] Consistently high levels of cortisol have been shown to increase intestinal permeability over time

★ **Slide 10-Pathos: Gut-brain axis**

- A third factor connected to depression is the gut-brain axis
- The gut microbiome is a vast and complex system composed of 10^{14} microorganisms making it more diverse than the human genome.[14] A diverse and dense microbiome has been found to be associated with a decreased risk of disease, whereas a less diverse or disrupted balance, also known as dysbiosis, is found to be associated with an increased risk of disease including depression
- The bidirectional communication between our enteric nervous system and central nervous system via the vagus nerve is known as the gut brain axis (GBA).[17] Disruption to the GBA can influence changes in gut microbiota composition, while modification of the microbiome can induce depressive-like behavior
- Alteration of the microbiome composition can promote gaps in the endothelial lining of the gut increasing intestinal permeability leading to a leaky gut. This can cause the translocation of certain Gram-negative bacteria, which can activate the immune system leading to a pro-inflammatory response
- Elevated levels of IgM and IgA in response to these circulating bacterial lipopolysaccharides (LPS) have been found in depressed individuals
- Additionally, fiber is an essential component of the gut microbiome because it is fermented by the bacteria in the gut creating an abundance of short-chain fatty acids (SCFAs), which are thought to be the primary mechanism of metabolic interactions between the microbiota and host.[18]

★ **Slide 11-Pathos: Monoamine Neurotransmitters**

- A final factor associated with depression involves the level of monoamine neurotransmitters
- The monoamine hypothesis proposes the deficiency or depletion of serotonin, norepinephrine or epinephrine in the CNS is associated with depression
- A diet deficient in certain nutrients, such as vitamins B6, B9, and B12, can impact synthesis of these neurotransmitters
- Many antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are designed to increase

monoamine neurotransmission. While antidepressant use has been shown to increase neurotransmitter levels within days, impact on depressive symptoms is found to take weeks or longer

- Nevertheless, antidepressants are found to be ineffective in up to 40% of individuals with over half of individuals that continue taking antidepressants not fully entering remission.[30] This indicates that a deficiency in monoamine neurotransmitters is not the only factor in the pathophysiology of depression, but instead likely includes a unique combination of multiple factors.

★ **Slide 12-Systematic Review: Intro**

- The next group of slides highlights the methods, results, discussion and conclusion of the systematic review.
- This systematic review focuses solely on the nutritional interventions that have been studied regarding depression.
- Nutrition is one modifiable factor that can increase risk of depression and has been shown to strongly influence an individual's susceptibility to disease.
- Although multiple pathways or dysregulation of these pathways can play a role, dietary consumption of all essential nutrients that are part of the etiology of depression is necessary.

★ **Slide 13- Systematic Review: Methods**

- This systematic review was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines and PICOS framework
  - Participants (P) = all adults aged 18+
  - Interventions (I) = dietary pattern, nutrient, supplement, herb, spice
  - Comparisons (C) = habitual diet, placebo
  - Outcomes (O) = reduction in depressive symptoms
  - Study Design (S) = systematic review
- The purpose of this review was to gather the evidence regarding nutrition intervention studies related to potential treatment or prevention of depression.
- The research question is: Can a targeted nutrition protocol be developed from this evidence?

★ **Slide 14- Systematic Review: Results (Flow Chart)**

- Our initial searches resulted in 1355 records, which were narrowed down to 153 full-text studies for review. 60 studies were excluded based on factors including,

but not limited to, duplicates, depressive symptoms not measured or reported, study length too short for dietary impact or excluded population. 93 studies met the quality criteria and were included.

- The 93 studies include randomized control trials, clinical trials and observational studies in peer-reviewed journals with adults over the age of 18 and published in 2005 or later. Inclusion criteria consisted of dietary pattern or nutrition intervention, depression outcome reported, and similar group treatment. Exclusion criteria consisted of low quality methodology, intervention period of less than 3 weeks, interventions that are not feasible or multiple intervention factors such as exercise, targeted weight loss (calorie restriction), missing both depression-specific screener and depression-specific outcome, pregnant or lactating women.
- Additionally, the Joanna Briggs Critical Appraisal quality checklists were utilized by appropriate study type to determine study quality.

★ **Slide 15-Systematic Review: Results (Dietary Patterns)**

- The following two slides show a summary of all of the results for the studies focused on dietary patterns or supplements intended to reduce risk of depression or depressive symptoms.
- These two slides include 85 of the 93 studies from the systematic review.
- The two charts here are intended to give a quick visual of the dietary pattern study results. The top chart highlights the RCT studies that had significant findings. Additionally, all observational studies were associated with decreased risk or incidence of depressive symptoms.
- The 5 RCT studies in the chart below had positive findings, but not significant in comparison to the control groups. One thing to note on the chronic disease management category is that the control group in one of the studies was a diabetes management diet, and both groups had improvement which may be why there wasn't a significant finding. But this does highlight that a healthier dietary pattern even intended for management of a chronic disease may also help improve depressive symptoms.

★ **Slide 16-Systematic Review: Results (Micros & Supplements)**

- Similar to the dietary patterns, the two charts show a quick visual of the positive findings. The RCT studies shown in the chart above had significant findings. Additionally, all observational studies were associated with decreased risk or incidence of depressive symptoms. The RCT studies in the chart below had positive findings, but not significant in comparison to the control groups.

★ **Slide 17-Systematic Review: Results (Overview Positive Association)**

- *While the charts show the clear indication that nutrition can play a role in the reduction of depressive symptoms or risk of depression, a few of the significant findings are highlighted here:*
  - While many of the dietary pattern studies found a double digit reduction in risk of depression or symptoms, one study found a 98% reduction in depression risk associated with highest adherence to a Med- style diet
  - Additionally, another study found an 80% lower risk of depression with the highest Alternative Healthy Eating Index scores
  - A study that looked at Vitamin B intake over three years found a 43% lower risk of depression in women with the highest level of B6 intake. Of note in this study is that they looked at consumption of B vitamins from food intake rather than supplements.
  - An observational study found a 25% lower risk of depression at follow-up in women who consumed two or more weekly servings of fish in comparison to women who consumed less than 2 servings.
  - A study observing flavonoid intake found an 18% reduction in depressive symptoms in individuals with the highest consumption of citrus. Also, individuals with the highest consumption of tea had a 12% significantly lower risk of depression
  - In addition to reduced risk of depression or symptoms, studies also found changes in microbiota, pro-inflammatory markers and amino acid levels
  - In one study, the healthier diet intervention group had a significant change in microbial diversity along with an increase in fiber, vegetable and milk consumption as compared to the control group
  - In an 8-week RCT, the flavonoid-rich group had a significant reduction in depression symptoms along with a significant increase in two bacterial species (*Lachnospiraceae and Bifidobacterium*)
  - A two year observational study of Vitamin B12 and folic acid supplementation found a larger decrease in homocysteine levels in the intervention group
  - Not only did Omega-3 and vitamin E co-supplementation in women with PCOS find a significant reduction in depressive symptoms, but the women also experienced a down-regulation in pro-inflammatory markers

★ **Slide 18-Systematic Review: Results (Negative Association)**

- The following 8 studies looked at a Western style, high glycemic index, and low protein diet and focused on a possible correlation to an increased risk of depression
- In this case, all RCT studies had significant findings. Additionally, all observational studies were also associated with increased depressive symptoms.

- *Negative association - On the right side we highlight a few of the most significant findings:*
  - 40% higher risk of depression in top quintile of fast food consumption
  - 38% higher depression score with high glycemic load (HGL) diet
  - 10% increase in the percentage of ultra-processed foods (UPF%) was associated with a 21% increased risk of depressive symptoms

★ **Slide 19-Systematic Review: Discussion (Dietary Patterns)**

- The table shown here summarizes some of the main discussion points from the systematic review with relation to dietary patterns. To highlight a few by category:
  - A high intake of plant foods has shown antioxidant and anti-inflammatory properties, which are found in dietary patterns such as Med-style and higher AHEI scores.
  - Also, polyphenols found in plant-based foods impact through positive alteration of the gut microbiota
  - The increase in fiber in a Med-style diet or other anti-inflammatory dietary pattern is also positively associated with brain health and reduction in severity of symptoms
  - Gliadin, the protein found in wheat, has been shown to induce zonulin release, which can lead to a temporary increase in intestinal permeability. Chronic exposure has been shown to downregulate tight junction gene expression. In patients with MDD, increased permeability has been found along with increased pro-inflammatory expression.
  - Immune cells in the gut become dysregulated with a processed diet, making the gut prone to inflammation.
  - Low-fiber diets, such as the Western diet often lead to an increase in inflammatory biomarkers.
  - Additionally, high glycemic index foods have also been correlated with increased cortisol levels, which can cause HPA axis dysregulation

★ **Slide 20-Systematic Review: Discussion (Nutrients)**

- The table shown here summarizes the main results of the studies that looked at specific nutrients and their effect on depression.
  - Depression-fighting nutrients such as B Vitamins, Vitamin D, magnesium, selenium, Omega-3s, and zinc play a role in reducing systemic inflammation, the regulation of the HPA axis, and monoamine neurotransmitter synthesis

★ **Slide 21-Systematic Review: Conclusion**

- While there are many significant findings, the conclusion of the data is summarized into three major bullets.

- The Mediterranean-style and anti-inflammatory dietary patterns, in addition to omega-3 supplementation were associated with the greatest improvements by potentially mitigating oxidative stress and systemic inflammation associated with depression.
- Supplementation of certain nutrients including amino acids, B vitamins, vitamin D, zinc, and magnesium were associated with a decrease in depressive symptoms potentially due to their involvement in monoamine neurotransmitter synthesis and overall neuroprotective benefits.
- Additionally, dietary intake of polyphenols, flavonoids, fiber, probiotics, low glycemic index foods and elimination of gluten were correlated with reduced depressive symptoms likely due to the improved tight junctions of the endothelial lining, regulation of the HPA axis, and the modification of the gut microbiota composition.
- Finally, based on the evidence, it can be concluded that a targeted nutrition protocol can be proposed for future study.

★ **Slide 22: ANA Poster Experience**

- We feel very fortunate to have gotten the opportunity to submit the abstract poster shown here to the American Nutrition Association. The ANA poster was an unexpected, but rewarding experience. With exceptional input from Professor Petrosky, we submitted a comprehensive abstract to the ANA Personalized Nutrition Summit for possible acceptance of a poster presentation. Although the selection of accepted abstracts was delayed putting us in a short timeframe, the final poster is a scientific presentation that we are extremely proud of. The process of writing and editing an abstract for potential acceptance along with creating the actual poster was a valuable hands-on experience for future work and opportunities. In addition, we put together a short presentation to highlight our poster and results giving us experience for future poster presentations.

★ **Slide 23: Proposed Nutrition Protocol Recommendations for Prevention and Treatment of DepressionProposed Nutrition Protocol Recommendations for Prevention and Treatment of Depression**

- From the evidence of the systematic review, a proposed nutrition protocol is being developed. The following slides highlight the nutrition and dietary intake components of the proposed protocol. We also highlight the additional factors that are to be included. In the future, we would like to have this protocol tested for feasibility and acceptability by participants. Based on preliminary results, the proposed protocol would be refined further.
- Nutrition is often overlooked for the prevention and treatment of depression while numerous studies have associated nutrition with a significant reduction in

symptoms. A well-balanced diet consisting of dark leafy greens, vegetables, fruit, whole grains, and healthy fats can reduce an individual's susceptibility to depression.

- The proposed nutrition protocol recommendations focus on the metabolic mechanisms associated with oxidative stress/inflammation, the gut-brain axis, and nutrient deficiencies associated with depression.
  - Goals:
    - Increase whole food consumption of fruits and vegetables by following an Anti-Inflammatory dietary pattern while avoiding ultra-processed foods and added sugars
    - Achieve and maintain optimal levels of essential nutrients for brain health such as, B vitamins, omega-3 fatty acids, zinc, selenium, vitamin D, and magnesium
    - Restore gut microbiome balance and digestion, absorption, and elimination functions by increasing fiber intake, consuming fermented foods, supplementing with probiotics and digestive enzymes, and limiting gluten
    - Increase nutrient antioxidants, such as vitamin C, vitamin E, carotenoids, polyphenols, and flavonoids to combat free radical production, oxidative stress, and inflammation
- On the right side, you can see the recommended food groups and nutrients, such as:
  - Foods rich in B vitamins
  - Dark leafy greens
  - Cruciferous vegetables
  - Omega-3 containing foods
  - Fermented and probiotic foods
  - Zinc-containing foods
  - Nuts, seeds, antioxidants, spices and herbs

★ **Slide 24: Proposed Dietary Protocol including daily servings by category along with vegetable and fruit charts.**

- The proposed protocol highlights servings daily or weekly by category. The protocol additionally lists the top nutrient foods for depression within each category. Each category on the left hand side has foods ranked by essential depression nutrients or dietary components. The column on the right hand side shows the nutrient or dietary component that was used to rank the foods. For example, in the legumes category, we ranked the top three legumes by fiber and also highlighted that they are a plant-based tryptophan source, another essential depression nutrient.

- In addition, vegetable and fruit categories are divided into two groups as shown here on the far right hand side. Group A dark greens are ranked by most nutrient dense per 1 cup serving and Group B is ranked by highest quantity of vitamins B6 and B9
- Additionally, the recommended 5 servings for vegetables and 3 servings for fruits includes 2 or more servings from group A and 2 or more servings from Group B to ensure adequate amounts of B vitamins, polyphenols, and flavonoids. It is also recommended to consume 2 servings daily of legumes and 2 servings daily of whole grains for fiber and other essential nutrients such as tryptophan and magnesium.
- 1 oz of nuts and seeds is also recommended for added selenium, magnesium and zinc.
- Protein sources should mainly come from fish rich in omega-3. Turkey, chicken, red meat and dairy should be consumed in limited amounts.
- In addition, 3 servings weekly of fermented foods is recommended for gut health, along with the frequent use of herbs and spices, and limited sweets, with the exception of 1-2 squares of dark chocolate daily for added magnesium and antioxidants.

★ **Slide 25: Proposed Dietary Protocol: Other intake**

- In addition to the recommended servings by category, other recommendations listed below are also included within the proposed protocol:
  - *For Protein Intake*
    - It is recommend to consume a minimum of .8g/kg
    - And also to regularly consume protein sources higher in tryptophan such as tofu, fish, turkey and chicken
  - *(Fiber):* It is recommend to consume a minimum of 38g of fiber daily for women and men
  - *Fluid Intake*
    - Adequate fluid intake is important for proper digestion and overall health. Increased intake of fruits and vegetables will add to fluid intake, but it is also recommended to consume
    - At least 10 cups or 80 fl oz of water daily, more can be consumed as needed based on activity level, temperature, pregnancy or breastfeeding
    - Fruit juice, soda or other sweetened beverages should be limited
  - *(Fats):* Consuming unsaturated fats such as olive oil, flax, walnut, and avocado is also recommended while avoiding saturated such as butter
  - *Added Sugar and Processed Foods*
    - Limit added sugars to 10g or less per day
    - Avoid processed and pre-packaged foods

- **Slide 26: Proposed Protocol: Additional Factors**
  - While the protocol only touches on nutrition, some additional factors we would like to do further research on include exercise and mindbody practices, such as meditation, yoga, and journaling
  - Exercise, in particular, has been shown to decrease the risk of developing depression. A 10-month study demonstrated that individuals in the exercise only group exhibited decreased depressive symptoms and were more likely to fully recover compared to the medication only and combined group
  - In addition, mindfulness-based stress reduction may also decrease risk by changing thinking patterns associated with depression

- **Slide 27: Sample Weekly menu**
  - The table below shows a sample weekly menu that includes meals consisting of foods from the proposed dietary protocol. The meals were created using foods containing key nutrients that play a role in optimal brain functioning. Each day includes the recommended daily servings for each category as well as the weekly recommended servings for each essential depression nutrient.
  - The sample menu also shows the variety that can be consumed with 14 different lunch and dinner options and an additional 7 breakfast options.
  - All days follow a primarily plant-forward diet rich in vegetables, fruits, whole grains, legumes.
  - As an example day, Monday is oatmeal w/ berries and banana, a snack of green pea hummus w/ veggies, a grains and greens bowl with tofu for lunch, berries and nuts for afternoon snack and salmon with mango salsa and a quinoa salad for dinner.
    - The berries, banana, beets, mango, green peas are included for B vitamins
    - Chickpeas, oatmeal, quinoa, and veggies for fiber
    - Salmon for omega-3s, B12 and essential amino acids
    - Tofu for soy and protein
    - Nuts and seeds for essential nutrients such selenium, magnesium and zinc

- **Slide 28: Nutrient intake overview for the sample weekly menu**
  - The data here shows a 3-day average of the sample menu entered into Cronometer.
  - All essential depression-fighting nutrients such as B vitamins, vitamin D, zinc, magnesium, selenium, and amino acids are shown to be in optimal range

- **Slide 29: Prototype educational materials**
  - Here we show two prototype educational materials for the Proposed dietary protocol. Our educational materials focus on essential depression nutrients or dietary factors such as fiber.

- Our educational materials aim to educate on why each food or nutrient is beneficial and also gives ideas or tips on use of these nutrients, ingredients or whole foods.
- Our green pea hummus recipe highlights the essential nutrients related to depression including B vitamins, fiber, Omega-3s, prebiotics and citrus
- This prototype also contains the recipe along with 3 suggested uses of the green pea hummus
- On the right hand side, the education prototype highlights that Salmon is a rich omega-3 source, high in protein, vitamins B and D along with almost 100% of the recommended daily selenium per 6 oz serving.

★ **Slide 30: Acknowledgements**

- We would like to thank Professor Petrosky for all of her guidance and support throughout this project. She challenged us and asked great questions early on to help guide us in our final direction. She has been a great mentor and resource not only for this project, but throughout our time in the program. Additionally, Professor Petrosky sent us the call for abstracts for the ANA poster. Her guidance and advice here helped ensure the successful acceptance of our poster at the ANA Personalized Nutrition Summit.
- We would also like to thank Dr. Robin Jacobs who provided valuable advice on our poster within a tight timeline. We are grateful for the advice she provided in a very timely manner. We are proud of our final poster and have both Professor Petrosky and Dr. Jacobs to thank.

★ **Slide 31: References**

Questions???

Rates of depression have been rising steadily over the last several decades with more than 264 million people affected globally as of 2019, making it one of the top three burdens globally. The pandemic has brought on a greater risk of depression with up to 42% of individuals surveyed by the US Census Bureau reporting depressive symptoms in December 2020. Many factors can play a role in the development of depression during traumatic events like the pandemic, and dietary factors such as reduced diet quality, were found to be correlated in many studies. A low-quality dietary pattern has been associated with obesity, low-grade chronic inflammation, dysbiosis, increased cortisol levels, reduced BDNF levels, and monoamine neurotransmitter deficiency, which have all been correlated with an increased risk of depression. Additionally, antidepressants have been shown to be ineffective in up to 40% of individuals. Therefore, the potential of a nutrition-focused approach should be considered. Due to the lack of targeted protocols found, a systematic review was conducted to determine if an evidence-based, targeted nutrition protocol could be developed for the prevention or treatment of depressive symptoms. The results of the systematic review strongly indicate certain nutrients and dietary patterns have the potential for the prevention and treatment of depressive symptoms. Utilizing the results of nearly 100 studies from the systematic review and additional research, a proposed nutrition protocol is being developed for presentation. The presentation of this comprehensive project will show the condensed systematic review results along with details of a proposed nutrition protocol that can be studied for the potential prevention and treatment of depressive symptoms.

Revised Abstract:

Rates of depression have been rising steadily over the last several decades with more than 264 million people affected, making it one of the top three burdens globally. The pandemic has brought on a greater risk of depression. 42% of individuals surveyed in December 2020 by the US Census Bureau reported depressive symptoms. Many factors, including poor diet quality, play a role in the development of depression during traumatic events like the pandemic. A low-quality dietary pattern has been associated with obesity, low-grade chronic inflammation, dysbiosis, increased cortisol levels and monoamine neurotransmitter deficiency. Among others, these factors have been correlated with an increased risk of depression. Additionally, antidepressants have been shown to be ineffective in up to 40% of individuals. Therefore, the potential of a nutrition-focused approach could be helpful. A systematic review was conducted to determine if an evidence-based, targeted nutrition protocol could be developed for the prevention or treatment of depressive symptoms. The results of nearly 100 studies strongly indicate certain nutrients and dietary patterns have the potential to reduce depressive symptoms. A proposed nutrition protocol was developed as a result and will be presented in this session along with the summary findings of this unique review.

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The project we are submitting for consideration is part of our final course for the Nova Southeastern graduate program in nutrition. The work is being completed under the mentorship of Professor Petrosky, head of the graduate M.S. Nutrition program.

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Background: Rates of depression have been rising steadily over the last several decades with more than 264 million people affected, making it one of the top three burdens globally. The pandemic has brought on a greater risk of depression. 42% of individuals surveyed in December 2020 by the US Census Bureau reported depressive symptoms. Many factors, including poor diet quality, play a role in the development of depression during traumatic events like the pandemic. A low-quality dietary pattern has been associated with obesity, low-grade chronic inflammation, dysbiosis, increased cortisol levels and monoamine neurotransmitter deficiency. Among others, these factors have been correlated with an increased risk of depression. Additionally, antidepressants have been shown to be ineffective in up to 40% of individuals. Therefore, the potential of a nutrition-focused approach could be helpful.

Purpose/Objectives: A systematic review was conducted to determine if an evidence-based, targeted nutrition protocol could be developed for the prevention or treatment of depressive symptoms.

Methods: The proposed nutrition protocol was developed from the results of nearly 100 studies that strongly indicate certain nutrients and dietary patterns have the potential to reduce depressive symptoms.

Results: The Mediterranean-style and anti-inflammatory dietary patterns were associated with the greatest improvements by potentially mitigating oxidative stress and systemic inflammation associated with depression. Supplementation of certain nutrients including B vitamins, vitamin D, omega-3 fatty acids, zinc, or magnesium were associated with a decrease in depressive symptoms.

Conclusions: A proposed nutrition protocol was developed from the summary findings of this unique review and will be presented in this session.

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Additionally, it has been found that 90% of the body's serotonin is produced by the enterochromaffin cells (EC) in the gut.[31]

FOR POSTER

Introduction

Rates of depression have been rising steadily over the last several decades with more than 264 million people affected, making it one of the top three burdens globally.[1] The pandemic has brought on a greater risk of depression. 42% of individuals surveyed in December 2020 by the US Census Bureau reported depressive symptoms.[6] Many factors, including poor diet quality, play a role in the development of depression during traumatic events like the pandemic.[5,7] A low-quality dietary pattern has been associated with obesity, low-grade chronic inflammation, dysbiosis, increased cortisol levels and monoamine neurotransmitter deficiency.[11,14-16,19-21,23-25,27,28] Among others, these factors have been correlated with an increased risk of depression.[3,9,10,16,26] Additionally, antidepressants have been shown to be ineffective in up to 40% of individuals.[30] Therefore, the potential of a nutrition-focused approach could be helpful.

Objective

A systematic review was conducted to determine if an evidence-based, targeted nutrition protocol could be developed for the prevention or treatment of depressive symptoms.

Methods/Materials

An electronic search was conducted in June 2021 using PubMed for its relevant inclusion of nutrition, health and science-related topics. This review includes published studies from 2005 or later with full text available, randomized control trials, clinical trials and observational studies in peer-reviewed journals in the English language with human adults. Inclusion criteria consisted of dietary pattern or nutrition intervention, depression outcome reported, and similar group treatment. Exclusion criteria consisted of low quality methodology, intervention period of less than 3 weeks, interventions that are not feasible or multiple intervention factors such as exercise, targeted weight loss (calorie restriction), missing both depression-specific screener and depression-specific outcome, pregnant or lactating women.

Results/Discussion

The results from the systematic review are summarized in the charts below. The dietary patterns and nutrients with the strongest level of evidence demonstrating protective benefits against depression have been included along with discussion points.

Dietary Pattern Results and Discussion

Dietary Pattern	Nutrients	RCT Study Results	Observational Study Results	Discussion
Mediterranean, Anti-inflammatory Diet & Alternative Healthy Eating Index	omega-3, B vitamins, vitamin D, zinc, folic acid, selenium, iron, dietary fiber, phytochemicals, vitamin C	A Med-style diet has been found to significantly reduce depressive symptoms compared to control group34-36FP	Med-style diet has been associated with lower depression scores with up to a 98% reduction in depression risk with highest tertile adherence38-41FP; High adherence to an anti-inflammatory diet (AID) has been associated with reduced depression risk while higher dietary inflammatory index (DII) has a positive correlation with increased depressive symptoms.76-81FP; An inverse relationship has been found between diet quality and lower depressive symptoms with up to 80% lower risk in individuals with the highest Alternative Healthy Eating Index51-61FP	High intake of plant extracts such polyphenols have been shown to possess antioxidant and anti-inflammatory properties.128FP Anthocyanins have been found to potentially mitigate oxidative stress and systemic inflammation.129FP,130FP; Polyphenols impact through alteration of the gut microbiota by acting as prebiotics, increasing beneficial bacteria132FP,133FP; Flavonoids exert anti-inflammatory responses altering cytokine expression and oxidative stress.134FP; Increase in fiber intake is positively associated with brain health and reduction in severity of depressive symptoms63FP,141FP,142FP ; Higher DII score has been correlated with an elevated risk of depression and increased concentration of circulating proinflammatory markers.162FP
Gluten-Free Diet	Habitual diet excluding gluten	A six-week gluten-free diet has been found to to significantly reduce depressive symptoms72FP		Gliadin, a protein found in wheat, has been shown to induce zonulin release, which can lead to a temporary increase in intestinal permeability. Even though the expression of permeability is not as great in non-celiac disease individuals, chronic exposure to gliadin was shown to downregulate tight junction gene expression regardless of genetic expression. In patients with MDD, increased zonulin-mediated permeability has been found along with increased pro-inflammatory expression.153 FP
Nut Consumption	folic acid, iron, niacin, vitamin E, vitamin B6, calcium, magnesium, potassium	An almond low carbohydrate diet was associated with a significant reduction in depressive symptom. In addition, an significant improvement in SCFAs in the gut microbiome was observed73FP	Higher consumption of nuts has been associated with a reduction in depressive symptoms74FP	Nuts contain many nutrients that are found to be beneficial for reducing risk of depression. Although selenium levels in food can vary depending on region and soil quality, higher protein foods, such as nuts, can be a rich dietary source of selenium. Selenium has been shown to play a role in risk of depression potentially via the attenuation of inflammation and also modulation of oxidative pathways and neurotransmitters.155 FP, 156 FP
Western-style Diet & Fast-food; High Glycemic Index	Varied based on actual intake - high processed and/or low vegetable & fruit consumption	Low glycemic load diet (LGL) has shown significantly lower depression score with up to a 38% higher score with high glycemic load (HGL) diet68FP	An increased risk of depression has been associated with a Western-style diet and increased frequency of fast food intake including up to a 40% increased risk in highest quintile of consumption82-87FP;Higher consumption of high glycemic foods was associated with an increased risk of depression69FP	Immune cells located in the gut become dysregulated by a diet high in sugar and fat, making the gut more prone to inflammation.163 FP Chronic inflammation of the gut results in inflammatory bowel diseases (IBD), which are associated with a higher risk of depression.164 FP Western-style diets are also low in dietary fiber. Low-fiber diets are also associated with depression because they often lead to an increase in inflammatory biomarkers such as IL-6 and IL-8. 165 FP Additionally, high GI foods have also been correlated with increased cortisol levels.24FP, 149FP

Nutrient Results and Discussion

Nutrient	Neurotransmitter	Inflammation Pathway	HPA axis Pathway	Neuroplasticity	RCT Study Results	Observational Study Results	Discussion
Vitamin A	Deficiency leads to reduced production of enzymes that make neurotransmitters	deficiency leads to the exacerbation of preexisting inflammationWiedermann 1996?	deficiency increases HPA activity and cortisol production3 (Nguyen, 2017)	Deficiency can lead to reduction in neurogenesis, neuronal survival, and synaptic plasticity	Vitamin A supplementation has been shown to significantly reduce depressive symptoms.88FP		Vitamin A is an effective antioxidant.167FP; Plays a role in immune competence helping with production of regulatory T helper cells and interacts synergistically with other nutrients important in risk of depression such as zinc.168FP,169FP
B Vitamins	Essential for the production of monoamines. 28FP, 146PP. Deficiency can lead to decreased levels of SAMe and neurotransmitter synthesis. 27FP	Deficiency can lead to high homocysteine levels promoting pro-inflammatory cytokines177P; Reduces oxidative stress in the brain.5 (Kamat,1999)		Deficiency can lead to reduced BDNF expression 6 (Rathod, 2016); Reduced BDNF expression negatively impacts neuroplasticity and neurogenesis13FP	Supplementation of folic acid has been shown to significatly reduce depressive symptoms89FP; Supplementation with folic acid and viatmain B12 has also been shown to decrease homocysteine levels90FP	Vitamin B6 supplementation was found to have a 43% lower risk of derpression in women. Vitamin B12 supplementation was shown to reduce derpession levels in men. 91FP	Folate is necessary for the modulation of monoamine synthesis.146FP; Levels may also be dose-dependent with severity potentially increasing with higher deficiency level.170FP; Low levels of vitamin B6 found to be associated with increased risk of depression.171FP; B6 is a cofactor for the production of serotonin,28P and deficiency levels have been correlated with severity of disease.172FP; Deficiency in B vitamins reduces the modulation of oxidative stress caused by elevated homocysteine levels.173FP, therefore an increase in oxidative species
Vitamin D	deficiency can lead to dysfunction in serotonin levels176FP	Deficiency can lead to upregulation of proinflammatory responses175FP		Vit D receptors control neurotrophic factors - deficiency may reduce neuroprotective benefits174FP	Supplementation with vitamin D has been shown to signficantly improve depressive symptoms92-94FP; Additional studies with co-supplementation of vitamin D and probiotics have also shown a significant reduction in depressive symptoms. 95,96FP		Several vitamin D receptors are present in the brain and control neurotrophic factors that may initiate neuroprotective benefits.174FP; D influences the immune system by downregulating proinflammatory responses while promoting anti-inflammatory pathways.175FP; Also aassociated with the formation of serotonin by promoting the expression of serotonin receptor, TPH2.176FP
Magnesium	NMDA receptors can be damaged with deficiency which can impact mood156FP	Deficiency associated with increased inflammation156FP	Deficiency can lead to dysregulation of the HPA axis and increase cortisol production156FP	deficiency associated with decreased neurogenesis and neural plasticity 156FP	Supplementation of magnesium has been shown to improve depression scores100FP	Supplementation of magnesium wasnegatively associated with depression. 101FP	Deficiency may be related to HPA axis dysregulation and increased systemic inflammatory response.156FP
Omega-3	deficiency can lead to dysfunctions in transmission of serotonin, norepinephrine, and dopamine 8 (Su, 2009)	reduces inflammation by preventing trans fats from entering the neural system	High evening cortisol levels associated with low n-3 PUFA levels185FP	associated with improvement in neuroplasticity, critical for neuron structure. 6 (Rathod,2016)	Supplementation with omega-3 fatty acids has been shown to significantly reduced depression scores and also associated with a significantly higher depression remission rates112-114,116FP; Additionally co-supplementation of omega-3 and vitamin E has been found to significantly reduce depression scores and also downregulate pro-inflammatory markers115FP		Help regulate the inflammatory response and have shown to be protective against mood disorders such as depression.19FP,184FP; Cohort studies have found an inverse relationship of low n-3 PUFA levels and increased levels of pro-inflammatory markers such as IL-6, TNF-alpha and CRP.185FP; Low n-3 PUFA levels have been associated with high evening cortisol.185FP, indicating potential HPA axis dysfunction with low levels
Selenium	Modulation of serotonin, noradrenaline, dopamine156FP	essential for the production of glutathione (a brain antioxidant)156FP	deficiency associated with dysregulation of oxidative and inflammatory pathways156FP	deficiency can lead to decreased BDNF concentrations7 (Mitchell, 1998)		Nuts contain high level of selenium. A higher nut consumption was associated with a reduction in depressive symptoms.74FP	Shown to play a role in risk of depression potentially via the attenuation of inflammation and also modulation of oxidative pathways and neurotransmitters.156FP
Zinc	Required for neurotransmitter production and brain enzymatic activity	Deficiency can lead to an increased inflammatory response156FP	Deficiency can increase cortisol levels156FP	Deficiency can decrease neuronal plasticity156FP	Zinc supplementation has been found to signficantly reduce depression scores compared to controls and also to multivitamin only supplementation;102,103FP Additionally supplementation has shown an inverse relationship between BDNF levels and severity of depression102FP		Strong support in the literature for the increased risk of depression with zinc deficiency partially due to its mood-enhancing effects.156FP; Deficiency associated with increased cortisol levels and decreased neuronal plasticity.156FP

Systematic Review Conclusions and Proposed Targeted Protocol

Proper nutrition has a significant impact on overall health and reduced risk of disease, likely from the potential to modulate pathophysiological factors in depression. Therefore, this review examined the evidence regarding nutrition intervention studies related to potential treatment and prevention of depression. The Mediterranean-style and anti-inflammatory dietary patterns, in addition to omega-3 supplementation were associated with the greatest improvements by potentially mitigating oxidative stress and systemic inflammation associated with depression. Supplementation of certain nutrients including amino acids, B vitamins, vitamin D, zinc, and magnesium were associated with a decrease in depressive symptoms potentially due to their involvement in monoamine neurotransmitter synthesis and overall neuroprotective benefits. Additionally, dietary intake of polyphenols, flavonoids, fiber, probiotics, low glycemic index foods and elimination of gluten were correlated with reduced depressive symptoms likely due to the improved tight junctions of the endothelial lining, regulation of the HPA axis, and the modification of the gut microbiota composition. Based on the evidence, it can be concluded that a targeted nutrition protocol can be proposed for future study.

Proposed Targeted Protocol

This proposed protocol is intended for the prevention of depression or as a complementary treatment for mild to moderate depression. It is not recommended to replace antidepressant medications unless specified by a physician. It is recommended for the essential depression nutrients to be consumed via food where possible. Due to the biochemical individuality of each person, supplementation for these nutrients may be recommended if needed under the supervision of a registered dietitian, certified nutritionist or physician. The proposed protocol below highlights servings daily or weekly by category. Each category has an intended serving recommendation along with top nutrient foods within each category. These foods are not the only recommendations, but shown for example as the top sources.

Dietary Component	Servings	Nutrient Ranking
Vegetables	5 or more servings daily	
Group A - Dark Greens	2 or more servings	B Vitamins, Polyphenols & Flavonoids
Group B - B Vitamin	2 or more servings	B Vitamins
Fruit	3 or more servings daily	
Group A- Berries	2 or more servings	B Vitamins, Antioxidants, Flavonoids
Group B- B Vitamin	1 or more servings	B Vitamins
Legumes	2 servings daily	Fiber, Plant-based tryptophan
chickpeas	Soy 1-3 times weekly	
navy beans		
lentils		
Whole Grains	2 servings daily	Fiber
quinoa		
oats		
gluten-free sprouted bread		
Fish	3 or more servings per week (6 oz)	Omega-3
Fatty Fish		
Nuts	1 serving daily (1 oz)	Se, Mg, Zn
brazil nuts		
cashews		
almonds		
walnuts		
Seeds	1 serving daily (1 oz)	Se, Mg, Zn
pumpkin / hemp		
sunflower		
flax / chia		
Turkey, Chicken	up to 1 serving daily (4oz)	Tryptophan, B12
Red Meat	up to 1 serving per week (3 oz)	B12, Tryptophan
Dairy	up to 1 serving daily	B12, Vitamin D, Tryptophan
eggs		
yogurt		
Herbs & Spices	Frequent use daily	Anti-inflammatory, Prebiotic
cinnamon, tumeric, ginger,		
garlic, lemon balm, rosemary,		
saffron, thyme, nutmeg		
Fermented Foods	3 servings weekly	pro- & prebiotics
kimchi, miso, tempeh,		
sauerkraut, pickled vegetables		
Sweets	1-2 squares daily	Antioxidants
dark chocolate-72% or higher		

Protein Intake

- Recommend minimum of .8g/kg
- Consume protein sources higher in tryptophan such as turkey, chicken, tofu, or fish

Fiber Intake

- Recommend a minimum of 38g of fiber daily for women and men

Fluid Intake

- Adequate fluid intake is important for proper digestion and overall health
- A diet higher in fiber intake requires an increased level of fluid
- At least 10 cups or 80 fl oz of water daily, more as needed based on activity level, temperature, pregnancy or breastfeeding
- 1-3 cups of coffee or tea daily
- Limited fruit juice, soda or other sweetened beverages
- Alcoholic beverages - limit to one per day for women or two per day for men
- Consuming the recommended servings of fruits and vegetables provides added fluid intake

Fats

- Consume unsaturated fats such as olive oil, flax, walnut, and avocado
- Avoid saturated fats such as butter

Added Sugar and Processed Foods

- Limit added sugars to 10g or less per day
- Avoid processed and pre-packaged foods
- Avoid artificial sweeteners
- Recommend natural sweeteners such as honey, maple syrup, and dates

Supplemental Charts

Vegetables Group A *Vegetables Group B*

Vegetables Group A - Dark Greens (2+ servings daily)
watercress
spinach
kale
mustard greens
swiss Chard
dandelion greens
lettuces
bok choy
spirulina
sea vegetables
brussel sprouts
broccoli

Vegetables Group B - Vit B6 + B9 Ranking (2+ servings daily)
avocado
green peas
bell peppers
artichokes
beets
corn
turnip greens
butternut squash
asparagus
cauliflower
sweet potato
carrots
mushrooms
tomatoes

Fruits (Berries) Group A

Fruits Group A - B6 + B9 Ranking (2+ servings daily)
boysenberry
elderberry
blackberry
strawberry
raspberry
blueberry

Fruits Group B

Fruits Group B - B6 + B9 Ranking (1+ serving daily)
bananas
mango
papaya
pomegranate
pineapple
oranges

Literature Cited/References

TO BE ADDED INTO POSTER

Disclosure/Acknowledgements

FOR PRESENTATION

Script

Hello, our names are Nicole and Camilla. We are graduate students in nutrition and we will be presenting our project, “A Systematic Review to Propose an Evidence-based Nutrition Protocol in Depression.”

Indtroduction

Our interest in this topic began with the realization that rates of depression are steadily rising, especially since the pandemic. Research shows a low-quality dietary pattern has been associated with obesity, low-grade chronic inflammation, dysbiosis, increased cortisol levels and monoamine neurotransmitter deficiency, which have all been correlated with an increased risk of depression. We believe the potential of a nutrition-focused approach could be helpful.

Therefore, this review examines the evidence regarding nutrition intervention studies related to potential treatment and prevention of depression to determine if an evidence-based protocol can be proposed.

Methods

Our systematic review was conducted using the search engine, PubMed. All randomized control trials or observational studies related to a dietary or nutrition intervention and impact on depressive symptoms were screened. From the search results, we selected 93 for inclusion in our systematic review.

Results

While most of the studies found significant results, we chose to highlight 50 studies here for their significant findings relative to our proposed protocol. The top chart shows categories associated with a reduction in depressive symptoms including anti-inflammatory dietary patterns and certain micronutrients. Contrastingly, the chart below is associated with an increase in depressive symptoms which included a Western-style diet along with high glycemic intake. We saw up to a 98% reduction in risk with a Mediterranean-style diet and up to a 40% increase in risk in the highest level of fast food consumption, showing significant dietary impact.

Discussion/Conclusion

Proper nutrition has a significant impact on overall health and reduced risk of disease, likely from the potential to modulate pathophysiological factors in depression. Our discussion and conclusion focus on the key factors associated with increased risk of depression including: modulation of systemic inflammation, improving the gut-brain axis and microbiome health and supporting the synthesis of monoamine neurotransmitters.

Based on the level of evidence supporting each of the pathophysiological factors of depression, it can be concluded that a targeted nutrition protocol can be proposed and developed for future study.

Proposed Targeted Protocol

The proposed protocol is intended for the prevention of depression or as a complementary treatment. It is not suggested to replace antidepressant medications unless specified by a physician. It is recommended for the essential depression nutrients to be consumed via food where possible. Due to the biochemical individuality of each person, supplementation of these nutrients may be

recommended if needed under the supervision of a registered dietitian, certified nutritionist or physician. The proposed protocol highlights servings daily or weekly by category. The full protocol additionally lists top nutrient foods within each category along with specific groups in vegetables and fruits, such as the one here.

It is recommended for future research to include testing of this proposed protocol.

Introduction

Rates of depression have been rising steadily over the last several decades with more than 264 million people affected, making it one of the top three burdens globally.[1] The pandemic has brought on a greater risk of depression, with 42% of individuals surveyed in December 2020 by the US Census Bureau reporting depressive symptoms.[6] Studies conducted during the pandemic, did show poor diet quality was a risk factor. Research shows a low-quality dietary pattern has been associated with obesity, low-grade chronic inflammation, dysbiosis, increased cortisol levels and monoamine neurotransmitter deficiency.[11,14-16,19-21,23-25,27,28] , which have all been correlated with an increased risk of depression.[3,9,10,16,26] With antidepressants shown to be ineffective in up to 40% of individuals, we believe the potential of a nutrition-focused approach could be helpful.

Therefore, we conducted a systematic review to determine if an evidence-based, targeted nutrition protocol could be developed for the prevention or treatment of depressive symptoms.

Methods/Materials

We searched in PubMed for all randomized control trials or observational studies related to a dietary or nutrition intervention and impact on depressive symptoms. Our search was narrowed down to 153 full text articles for review. Of these, we selected 93 for inclusion in our systematic review. Do we need a sentence listing a couple inclusion or exclusion factors?

Results/Discussion

While many of the studies found significant results, we chose to highlight 50 studies here for their significant findings related to depression. On the top we show the categories associated with a reduction in depressive symptoms including anti-inflammatory dietary patterns and micronutrients selenium, B vitamins, D vitamin, omega-3, magnesium and zinc. Contrastingly, we show the studies below associated with an increase in depressive symptoms which included a Western-style diet and fast food consumption along with high glycemic intake. A few of the most significant results were a 98% reduction in risk with a Mediterranean-style diet, 80% reduction with the Alternate Healthy Eating Index pattern and 43% reduction associated with the highest intake of B6. The highest level of fast food intake was associated with a 40% increase in risk and the highest glycemic intake was also found to show a 38% increased risk.

Discussion and Conclusions

Proper nutrition has a significant impact on overall health and reduced risk of disease, likely from the potential to modulate pathophysiological factors in depression. Therefore, this review examined the evidence regarding nutrition intervention studies related to potential treatment and prevention of depression. The Mediterranean-style and anti-inflammatory dietary patterns, in addition to omega-3 supplementation were associated with the greatest improvements by potentially mitigating oxidative stress and systemic inflammation associated with depression. Supplementation of certain nutrients including amino acids, B vitamins, vitamin D, zinc, and magnesium were associated with a decrease in depressive symptoms potentially due to their involvement in monoamine neurotransmitter synthesis and overall neuroprotective benefits. Additionally, dietary intake of polyphenols, flavonoids, fiber, probiotics, low glycemic index

foods and elimination of gluten were correlated with reduced depressive symptoms likely due to the improved tight junctions of the endothelial lining, regulation of the HPA axis, and the modification of the gut microbiota composition. Based on the evidence, it can be concluded that a targeted nutrition protocol can be proposed for future study.

Proposed Targeted Protocol

This proposed protocol is intended for the prevention of depression or as a complementary treatment for mild to moderate depression. It is not recommended to replace antidepressant medications unless specified by a physician. It is recommended for the essential depression nutrients to be consumed via food where possible. Due to the biochemical individuality of each person, supplementation for these nutrients may be recommended if needed under the supervision of a registered dietitian, certified nutritionist or physician. The proposed protocol below highlights servings daily or weekly by category. Each category has an intended serving recommendation along with top nutrient foods within each category. These foods are not the only recommendations, but shown for example as the top sources.

Afternoon preferred.

Nov 17, Nov 10,

Nov 24 - available if OK for faculty (as Tday is next day).