IMPACT OF WHOLE FOOD AND SUPPLEMENTATION ON MENTAL HEALTH DISORDERS:

A SYSTEMATIC REVIEW OF THE LITERATURE

A Dissertation

Presented to the Faculty of

Antioch University Santa Barbara

In partial fulfillment of the degree of

DOCTOR OF PSYCHOLOGY

by

Russell W. French
ORCID Scholar No. 0000-0002-5583-4008

May 2022

IMPACT OF WHOLE FOOD ON MENTAL HEALTH DISORDERS: A SYSTEMATIC REVIEW OF THE LITERATURE

This dissertation, by Russell W. French has

been approved by the committee members signed below who recommend that it be accepted by

the faculty of Antioch University Santa Barbara

in partial fulfillment of requirements for the degree of

DOCTOR OF PSYCHOLOGY

Dissertation Committee:

Brett Kia-Keating, Ed.D., Chairperson

Christina Donaldson, Ph.D., Second Reader

Kelli Davis, PhD., External Expert

ABSTRACT

IMPACT OF WHOLE FOOD AND SUPPLEMENTATION ON MENTAL HEALTH DISORDERS: A REVIEW OF LITERATURE

Russell W. French

Antioch University Santa Barbara

Santa Barbara, CA

This systematic literature review explores the relationship between mental disorders and nutrition through a review 547 available articles. Of these, 74 were selected for inclusion in this review. The research question guiding this inquiry was: What is the effect of nutrition on the mental health of individuals in the United States? A PRISMA flow diagram was used to develop systematic assessments of the existing research to produce a dataset of literature to answer the research question. It was found that nutrition and health are critically linked, with supplements being associated with positive health outcomes. It was also found that research is shifting to focus on the connection between the gut and the brain. The culmination of this review is that nutritional changes and support can positively impact anxiety and depression, and probiotic treatments have been linked to better dopamine regulation. Each disease is reviewed in relation to existing evidence on nutritional supplements that impact health symptoms. The findings of this review indicated that nutrition could have a notable impact on managing health conditions. It is recommended that models for health and nutrition be updated to encompass nutritional issues in the treatment of mental health disorders with a critical focus on patients' nutritional intake.

IMPACT OF WHOLE FOOD AND SUPPLEMENTATION ON MENTAL HEALTH DISORDERS

Keywords: nutrition, nutritional supplements, systematic literature review, mental health, whole foods, repairing neurotransmitters, major depression, generalized anxiety disorder, bipolar disorder, schizophrenia, food desert, eating disorders, racial and ethnic groups, diversity, inclusion, inequality, gaps in research

Table of Contents

List of Tables

List of Figures

Chapter I: Introduction

In the United States, 46.4% of individuals will experience a form of mental illness during their lifetime (National Institute of Mental Health [NIMH], 2019). A mental disorder is a condition in which an individual's psychological wellbeing deteriorates to the extent of causing significant distress or impairment in their behavioral, cognitive, and emotional functioning (NIMH, 2019). As of 2017, 50 million individuals suffered from various mental disorders, such as major depression, generalized anxiety disorder, post-traumatic stress disorder (PTSD), and obsessive-compulsive disorder (OCD). Individuals who suffer from mental health conditions are also at an increased risk of suicide in the United States (National Alliance on Mental Illness [NAMI], 2019; NIMH, 2019). Economically, the mental health burden has created $193.2 billion in lost earnings in the United States (NAMI, 2019). Globally, loss of productivity due to mental health disorders has led to a $1 trillion loss (NAMI, 2019; NIMH, 2019). Resultantly, the mental health burden on individual and economic health is a critical concern in academic research.

Examinations regarding mental health and nutrition are critical due to the increasing global economic and health burden (NAMI, 2019; NIMH, 2019). In the existing literature, the most common risk factors associated with mental disorders include genetics, physical injury, chronic disease, drug use, and environmental conditions (e.g., unhealthy home environments). In addition, however, researchers have noted that the type of food consumed is a significant determinant of mental wellbeing. A daily supply of all nutrients effectively reduces persistent symptoms of stress and mental disorders such as, depression, anxiety, and schizophrenia (Adan et al., 2019; Davidson et al., 2017; Petroaie et al., 2018; Sharma & Reddy, 2019). Nutritional supplements, such as minerals, vitamins, and fatty acids, may prove to be an effective approach

for alleviating symptoms of various mental disorders such as depression and anxiety (Kate et al., 2017; Naidoo et al., 2018).

Research Problem

Mental disorders affect a significant percentage of the American population (Greenwood et al., 2018; Mazza et al., 2019; NAMI, 2019; NIMH, 2019; Imtiaz et al., 2018; Xu et al., 2019). Researchers have posited that nutritional supplements are an effective intervention for reducing certain types of mental disorders (Adan et al., 2019; Davidson et al., 2017; Petroaie et al., 2018; Sharma & Reddy, 2019). Ideally, mental health could be effectively regulated through foods consumed (Davidson et al., 2017; Watson, 2017). The problem is that there is evidence to suggest a connection between diet and mental health; however, a thorough review of academic literature is needed to examine which dietary intervention can improve mental health. A systematic review will ideally illustrate the current state of research into the relationship and highlight current findings on the topic. The guiding research question is as follows: What is the effect of nutrition on the mental health of individuals in the United States?

Chapter II: Research Method

Methodology and Design Rationale

Through a systematic review, the researcher addresses a research question by identifying, critically evaluating, and synthesizing existing knowledge on a topic using peer-reviewed literature (Tracy, 2019). A systematic review is appropriate for addressing a previously understudied topic or clarifying an existing phenomenon (Baumeister & Leary, 1997). A systematic review aids the researcher in the identification of gaps, contradictions in previous literature, and information that furthers the understanding of a specific phenomenon (Bem, 1995; Cooper, 2003). From this information, the researcher can assert a general statement regarding the state of existing literature that addresses the current research question (Tracy, 2019). Systematic reviews do not fall squarely under quantitative or qualitative methodologies. A systematic review is a research process intended to address a specific research question based on existing literature (Tracy, 2019). For this process, the researcher may use quantitative, qualitative, or mixed methodology studies for inclusion in their research. However, clear criteria for including or excluding specific literature must be established prior to conducting the assessment (Baumeister, 2013).

Data Collection

Data collection was conducted by reviewing existing search engines and databases that included literature pertinent to the current research question. The steps that guided data collection are demonstrated in Table 1.

Table 1

Data Collection Process

Step	*Process*
1.	Define research question
2.	Based on the research question, set a series of inclusion and exclusion criteria.
3.	Create a PRISMA statement to illustrate the exact model used for the literature search.
4.	Locate studies
5.	Select studies
6.	Assess study quality
7.	Extract data from studies using the collection data sheet constructed for this study.
8.	Analyze and present results.

The research question was used to design the PRISMA flow diagram for this process. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) is a commonly used model for systematic assessments (Tracy, 2019). The PRISMA checklist was used to guide the data collection and analysis process (Appendix A). Further, the PRISMA checklist was used for data collection, and the literature search strategy discussed in the following section (Appendix B). For data collection, a pre-set list of databases was selected and a set of pre-set search terms specific to the purpose of the study (Appendix C). The search terms and databases were used for finding and assessing appropriate literature. The following PRISMA flow diagram was used to demonstrate the databases used, studies excluded, and the final tally of studies relevant to this study's purpose (Figure 1).

The researcher included both Google Scholar and proprietary search engines and search databases to generate a sufficient number of studies to be included in the review. These studies were updated within a PRISMA flowchart, which consists of a record for the data from each of the studies and documents the data collection process. All articles collected for the study were

published peer-reviewed journal articles generated over the last ten years (e.g., 2010 to 2020). Data included peer-reviewed sources, books, and dissertations to ensure that all relevant information was surveyed. Resultant data were presented according to the form of publication (e.g., peer-reviewed, book, or dissertation) to ensure that the readers were aware of the research form.

The search strategy for this literature review included searching the following academic databases: Google Scholar, Science Direct, and SpringerLink. The following keywords were used to locate relevant literature: *mental health, mental health disorders, neurotransmitters, systematic review, nutrition, diet, whole food, nutrition AND mental health disorders, nutrition AND schizophrenia, nutrition AND anxiety disorder, nutrition AND depression, whole food AND mental health disorders, mental health disorders, nutrition and mental health, bipolar disorder, major depression, schizophrenia, anxiety disorder, dopamine, and serotonin in mental health.* Articles published between 2016 and 2019 were included for review. The same set of key words was run in every database. The article search revealed 73 peer-reviewed research articles, with 92% of the reviewed literature from the past five years. Further, only 7% of the reviewed literature was prior to 2016. 45 articles were found from Google Scholar, 20 from Science Direct, and 8 from SpringerLink. Articles prior to 2016 were utilized due to their significance to the seminal literature on this topic.

Data Analysis

The data from the reviewed studies are presented narratively. Given the anticipated mixture of qualitative and quantitative data, the researcher anticipated examining the existing conclusions as presented within primary research studies and synthesizing these by assessing the methodologies employed, population studies, interventions used, and outcomes assessed. The

PRISMA flowchart (Appendix A) was used to record the final studies included and excluded. The original database searches were saved to ensure credibility (Appendix C). The data obtained was described in detail to ensure the data collection and analysis process (Appendix B). After final data collection, the results were presented and used to address the research question posed for this study.

Limitations

There were multiple limitations to this current study. No matter how rigorous, a systematic review cannot overcome design flaws conducted in the primary research upon which the review is based. The review cannot overcome biases in the literature. However, the researcher attempted to limit biased data by paying attention to publications with dramatic effects found in the data. The presence of potential bias in the data of various studies may limit the generalizability of the final systematic review. While the researcher assumed a consistent, fair evaluation method for each article, the techniques fluctuated across studies because the type and quality of data available varied. Weaknesses in any of the studies used in the systematic review of the literature may have limited the review's conclusions.

Further, the reliability of quantitative and qualitative data was also challenged. Data may have been coded differently across various qualitative studies, which would hinder how researchers reached conclusions regarding the same phenomenon. A lack of consistency in coding may mean that conclusions reached from qualitative data may not have been entirely reliable, therefore limiting the generalizability of the findings.

Assumptions

One of the researcher's assumptions in collecting literature for the systematic review was that there were consistent evaluation techniques used across multiple studies. Whether dealing

with quantitative or qualitative reviews, while the researcher attempted to make the best judgment possible about the literature retained for inclusion, the underlying assumption was that information in the included studies was fairly evaluated rather than unnecessarily influenced by the researcher. The researcher also assumed a certain consistency in evaluation and coding in the cases of qualitative studies. Qualitative studies rely on the interpretive judgment of researchers, but this researcher assumed that, in this instance, coding had been applied relatively consistent across studies.

Researcher Position

As a vegan, the researcher is focused and reliant on whole foods through a plant-based diet. Based on the researcher's previous experience, they find that a whole food plant-based diet is best. However, their convictions may not align with what the research reflects. The information reflected in this dissertation was produced to share the most empirically guided research results and do not reflect the researcher's personal beliefs and opinions. Instead, the presentation of the results of this study provided an overview of the most empirically based findings regarding mental health and nutrition.

Summary

The purpose of the current research study was to examine the relationship between nutrition and mental health. This research study relied on a systematic review of the literature. All studies included were drawn from the last ten years and included peer-reviewed sources, books, and dissertations. In Chapter Three, the researcher presents the results of the systematic review.

Chapter III: Results

The present systematic literature review has aimed to understand the relationship between nutrition and mental health. The PRISMA protocol was utilized to obtain articles to complete this review. The total records identified through database search were 547 eligible articles. A total of 351 articles were excluded from the initial identified 547 articles. The removed articles were excluded if they did not follow the a priori exclusion and inclusion criteria. The inclusion and exclusion criteria were represented in Chapter Two. A total of 74 articles were identified for eligibility as full-text articles. These final 74 articles were reviewed, which resulted in 33 articles being excluded after examination and comparison with the inclusion and exclusion criteria (Appendix G). For example, in some excluded articles, the nutritional and supplementation analysis was based on post-partum psychosis or mental health disorders resulting from cystic ovary development in female populations. In such cases, the articles were removed as they did not meet the inclusion criteria. Further, the nutritional and supplementation analysis was focused on treating or addressing medical issues associated with gynecological concerns, which were not directly related to mental health. A final sum of 41 articles was delineated and logged to be included in the final discussion of the systematic review results.

Nutrition and General Mental Health

Previous literature regarding diet and mental health is discussed in this chapter through eleven sections: (a) nutrition and mental disorders, (b) mental health and nutritional supplements, (c) dopamine, (d) serotonin, (e) the gut-brain axis, and mental health, (f) nutritional therapies for mental disorders, (g) whole foods for mental health disorders, (h) nutrition and bipolar disorder, (i) nutrition and major depressive disorder, (j) nutrition and schizophrenia, and (k) nutrition and anxiety disorder. Finally, a summary is presented to conclude the literature review. Before

initiating the discussion of academic investigations, the researcher presents the conceptual framework and search strategy. First, the conceptual framework that guided this study is presented in the following section.

In considering the reviewed literature, it is also important to note that the focus of this study was on dietary and supplementary shifts for mental health symptom alleviation. However, this does not consider the impact of medication, which is vital for many patients suffering from mental health illnesses. For example, patients with severe mental illnesses such as schizophrenia require medication to aid in performing a regular and healthy lifestyle (Cockburn et al., 2017; Velligan et al., 2017). Thus, while it is important to note that diet and supplements can aid mental health symptomology, it should not be considered a methodology preferred over the use of physician-prescribed medication. In addition, limitations of the dietary and supplementary approach are also discussed, which includes the consideration of individuals' inability to afford and access such dietary changes.

Conceptual Framework

The conceptual framework adopted for this literature review was drawn from concepts concerning the association between mental health and nutrition. Generally, mental health is characterized by a communication breakdown between neurons, thus altering the homeostatic balance that keeps an individual mentally healthy (Lakhan & Vieira, 2010). Essentially, communication between neurons is achieved by using neurotransmitters such as dopamine, serotonin, and acetylcholine, among others (Delvecchio et al., 2016). People tend to exhibit mental instability whenever there is a lack of balance in any one or multiple types of neurotransmitters in their system (Ross, 2018). For instance, when an individual has diminished serotonin levels, they are likely to exhibit symptoms of depression such as low moods and social

withdrawal (Demelash, 2017). On the contrary, slightly increased serotonin levels have been associated with happiness and mental stability dependent upon the patient and the context (Demelash, 2017).

Nutrition and Mental Disorders

Anxiety and Depression Symptom Reduction

Symptoms of anxiety and depression were reduced with the use of vitamin D, B-vitamins, probiotics, magnesium, lysine, arginine, myo-inositol, and N-acetyl-cysteine (Camfield et al., 2017; Kehr et al., 2018; McEwan & Fenasse, 2019; Watson, 2016). First, vitamin D plays a major role in regulating mood and the brain's general health (McEwan & Fenasse, 2019). Researchers have argued for a positive relationship between vitamin D and reducing depression symptoms (Berridge, 2017; Watson, 2016). In particular, vitamin D is associated with mild anxiety and depression symptoms (Berridge, 2017; Watson, 2016). Vitamin D is produced when the skin is exposed to sunlight. The main source of vitamin D in food is fatty fish, such as mackerel (Watson, 2016). Geng et al. (2019) provided a recent examination of vitamin D application for mental health disorders. First, vitamin D receptors (VDRs) are located in the Central Nervous System (CNS). These receptors are noted to be critical for distribution throughout the brain, which ultimately affects the reduction of depressive and anxiety-related symptoms. The receptors also aid in conducting vitamin D across the blood-brain barrier for binding to regions within the hippocampus. However, multiple human clinical trials have illustrated that doses of a minimum of 20ng/mL of vitamin D can be effective for symptom reduction (Geng et al., 2019).

Vitamin B Supplementation

Vitamin B complex is another nutrient that helps in reducing mental disorders. Vitamin B is composed of eight nutrients that coordinate to manage several processes within the body (Watson, 2017). Individuals who have low vitamin B-12 have high chances of experiencing anxiety or depressive symptoms. Mikkelsen et al. (2017) performed a systematic review between vitamin B and mental health disorders and illustrated the effectiveness of the treatment model. Firstly, the authors noted that vitamin B is crucial for DNA synthesis, maintaining and repairing phospholipids, regulating memory function, and reducing cognitive impairment. The authors stated that vitamin B should be used in association with treatment regimens such as therapy and medication to reduce the symptoms of depression. For reducing depression symptoms, the glutamate and Gamma-Aminobutyric Acid (GABA) neurotransmitters are linked to the uptake of vitamin B. Further, vitamin B is central in the methylation mechanism, a stress reduction response coordinated through methylation pathways and neurotransmitters. Overall, vitamin B appears to play a role in reducing stress and symptomology of depression through targeting poorly functioning cognitive neurotransmitters (Mikkelsen et al., 2017).

Probiotic Treatment

Dopamine Regulation

According to Ramos-Lopez et al. (2018), excessive consumption of sugary foods reduces dopamine levels. The resultant effects of reduced dopamine include memory loss, forgetfulness, and confusion. However, the arguments developed by Ramos-Lopez et al. do not establish a strong connection between food intake and mental health. Instead, the results only indicated symptoms of mental health challenges resulting from intake of foods rich in excessive amounts of sugar.

Dopamine balance has recently been considered an essential variable in regulating mental health. Deficiency is linked to Parkinson's disease, bipolar disorder, and schizophrenia (Grace, 2018). Grace provided an examination of dopamine deficiency and linked the absence of dopamine to schizophrenia. For example, dopamine secretion is critical to modulating motor behavior cognitive and emotional responses (Grace, 2018).

Serotonin Regulation

Serotonin is another important neurotransmitter strongly associated with feelings of happiness and general wellbeing (Lacasse & Leo, 2005). As such, high serotonin levels are desirable for positive mental health development. There is no one specific choice from the four main food groups—fats, proteins, carbohydrates, and vitamins—that collectively enhance the secretion of serotonin (Benton et al., 2017; Gibson, 2018). Empirical research, however, has illustrated that specific food groups facilitate the production of serotonin when consumed in moderate amounts (Benton et al., 2017; Gibson, 2018; Seyedi et al., 2019). The specific foods associated with high serotonin levels include fish, avocado, eggs, fruits, and low-fat cheese (Benton et al., 2017; Gibson, 2018; Seyedi et al., 2019).

There is an absence of research, however, identifying which food groups provide the most efficient serotonin levels to reduce mental health symptoms. For instance, Barth et al. (2017) associated relatively lower serotonin levels with the consumption of alcohol, caffeine, or sugar. Conversely, Yang et al. (2019) reported relatively higher levels of serotonin in mice that consumed higher levels of caffeine. These findings indicated a positive correlation between caffeine intake and serotonin levels. To account for the differences in the findings reported by Barth et al. and Yang et al. regarding caffeine intake and serotonin levels, Henry (2020) argued

that caffeine leads to only a temporary increase in serotonin levels that eventually prohibits the production of serotonin.

Similarly, Aggarwal et al. (2016) reported relatively higher serotonin levels in individuals who had a habit of consuming a balanced diet and correspondingly low serotonin levels in people who had developed a tendency of consuming an unbalanced diet. While Aggarwal et al. provided compelling evidence for the association between a balanced diet and higher serotonin levels, findings are not currently replicated in academic literature. To conclude, there is some evidence in previous assessments that have illustrated that diet affects serotonin levels, which can also impact mental health outcomes (Henry, 2020, Herrera et al., 2017; Holloway, 2016). However, there is a lack of academic understanding regarding the specific foods that are ideal for increased serotonin levels. Further, there is a lack of examining how nutritional supplements (e.g., vitamin B or D) contribute to serotonin uptake. Thus, further examination of the current literature is needed to assess the academic consensus regarding the correlation between serotonin and dietary supplementation.

Whole Food and Mental Health Disorders

Nutritional supplements, such as vitamins, can provide needed nutrients to the body (Gardner, 2018). Ideal consumptions, however, are through whole foods (Gardner, 2018; Mayo Clinic, 2019). In particular, nutritional supplements are less effectively absorbed by the body and are frequently filtered through an individual's urine (Gardner, 2018; Mayo Clinic, 2019). Further, whole food consumption provides increased essential fiber, complex micronutrients, and protective substances that slow cell and tissue damage (Gardner, 2018; Mayo Clinic, 2019). As such, consuming a diet that provides key nutrients is one model that can alleviate mental health symptoms (Gardner, 2018; Hunter & Hegele, 2017).

Amino Acids

Neurotransmitters are also empirically linked to mental health regulation and symptomology improvement (Briguglio et al., 2018; Nair, 2020). Neurotransmitters are categorized into six types: amino acids (e.g., memory and anxiety), peptides (e.g., endorphins), monoamines (e.g., sleep, depression, and motivation), purines (e.g., sleep and sensory control), gasotransmitters, and acetylcholine (e.g., motor neurons, learning, and memory; Briguglio et al., 2018; Nair, 2020; Noseda et al., 2017). Food consumption can further the creation of hormone production by neurotransmitters that impact mental health. In particular, food intake is associated with efficient regulation of acetylcholine, amino acids (e.g., GABA), and the production of dopamine and serotonin (Briguglio et al., 2018; Nair, 2020). Resultantly, researchers have reported that the consumption of fruits, plant-based foods, and botanicals increases key receptors hormones' production and impacts individual mental health (Briguglio et al., 2018; Nair, 2020).

Zinc

One example of key receptor hormones and their relation to mental health is zinc and mental health disorders. Zinc can be consumed through beans, green vegetables, mushrooms, nuts, cocoa, and some meat (Sarris & Firth, 2018). Conversely, lack of zinc is associated with poor mental health and reduced developmental growth in adolescents (Abradoh & Alwahaidi, 2019). Sarris and Firth argued that consuming micronutrients, such as zinc, through food intake was crucial to increasing individual mental health status. Basharat et al. (2019) also noted that zinc consumption through whole foods is ideal for increased mental health and decreased poor mental health outcomes. Grønli et al. (2013) also supplied empirical evidence of the impact of zinc on mental health disorders. In an assessment of 100 psychogeriatric patients, the authors applied the Depression Rating Scale and Mini-Mental State Examinations in combination with

the blood assessment of each patient. The same findings were compared with a control group of 882 individuals. Grønli et al. indicated that the patient group was more likely (41.0%) to have a zinc deficiency than the control group (14.4%), thus indicating that zinc deficiency can be one commonality in mental health disorders, which may be assisted through some form of supplementation or dietary changes (Grønli et al., 2013)

Magnesium

Similarly, magnesium is found in leafy green vegetables, whole grains, fish, nuts, and beans (Sarris & Firth, 2018). Researchers have noted that magnesium consumption through whole foods improves mental health (Bahramy et al., 2020), assists in symptoms of substance abuse recovery (Ordak et al., 2017), and decreases symptoms of depression (Tarleton et al., 2019). Notably, Tarleton et al. performed a cross-sectional analysis of medical records from 3,604 patients to examine the relationship between magnesium intake and depressive symptoms. The authors found that low-serum magnesium was associated with depressive symptoms. Supplementation of magnesium, however, assisted in the reduction of depression symptoms. Overall, researchers emphasize the importance of magnesium intake, ideally through whole foods, to reduce mental health symptoms (Tarleton et al., 2019).

Omega-3 and Cysteine

Individuals who suffer from bipolar disorders notably benefit from cysteine and Omega-3 (Jonsson, 2018; Ozdogan et al., 2020; Petrov et al., 2017; Petrov et al., 2018). Cysteine can be found in chicken, turkey, cheese, yogurt, eggs, sunflower seeds, and legumes. Further, Omega-3 can be obtained from fish, nuts, and seeds (Caires et al., 2017; Eratte et al., 2018; Gronroos, 2017; Shariat et al., 2020). Researchers have also noted that depressive symptoms can be reduced through B-vitamin or Omega-3 (Bjelland et al., 2009; Messaoudi et al., 2011; Ramsey,

2017; Saeed et al., 2007). These can be obtained through whole foods, such as whole grains, meat, eggs, legumes, seeds, and dark leafy green vegetables (Gibson et al., 2020; Li et al., 2017; Opie et al., 2017).

In sum, nutritional supplements are one model for increasing intake of key nutrients; however, whole foods are found to be more effective for introducing micronutrients that contribute to the furthered secretion of hormones signaled by neurotransmitters (Hunter & Hegele, 2017; Gardner, 2018; Mayo Clinic, 2019). Multiple researchers have indicated that plant-based diets, or general consumption of leafy green vegetables, nuts, eggs, and some meat, contribute to the micro and macronutrients that reduce symptoms of mental health disorders (Briguglio et al., 2018; Nair, 2020). Most commonly, zinc, magnesium, and Omega-3 are useful for whole food consumption (Bahramy et al., 2020). Ideally, future researchers will conduct empirical investigations regarding whole food consumption and mental health disorders for patients' bettered nutrient and dietary recommendations.

Limitations of Diet and Mental Health

This chapter was important to discuss a complete synthesis of the literature that represents a holistic review of diet and mental health interaction. While researchers have delineated a clear link between diet and mental health (Gómez-Pinilla, 2008; Lim & Kwak, 2019; Parra et al., 2018), some noted limitations to this argument that should be noted be detailed. One important argument to consider is that, despite the importance of diet, mental health issues can decrease an individual's ability to access healthy foods within their pay range (Acharya & Agius, 2017). For example, if an individual is disabled due to mental illness, they may not be able to afford or access healthy foods and nutritional supplements. The related phenomenon is described as a food desert and critically affects sufferers of mental illness and

disabled populations (Acharya & Agius, 2017). Additionally, is important to acknowledge the sociocultural and demographic factors that potentially influence access to healthy foods, nutritional supplements, and mental health symptomology (Dhillon et al., 2019; Jones et al., 2021). In particular, in the United States, African American and Hispanic populations lack access to healthy foods and nutritional supplements due to socio demographic disparities (Crowe et al., 2018; Teste & Jackson, 2019). Further, mental health symptomology is substantially high amongst minority populations that are contemporary and historically denied equal access to healthcare, mental health support, and other social support systems that can overcome racial inequalities in the United States (Dhillon et al., 2019; Jones et al., 2021).

A secondary limitation to diet as a treatment for mental health issues is eating disorders, or comorbidities between mental health disorders that influence nutritional and whole food intake (McArdle, 2019). Mental health disorders include eating disorders and compound the difficulty of eating a restricted or low-calorie diet (Draper et al., 2019; McArdle, 2019). Researchers have suggested that healthy diet considerations for mental illness are considered within the patient's ability to consume food in a non-restrictive manner that also meets caloric intake needs (McArdle, 2019). Thus, a dietician or physician should closely consider what is possible for the patient, especially if a history of an eating disorder is present in the patient's history.

Research has also indicated that while dietary and nutritional supplements may aid mental health symptoms, limitations should be considered. According to Teasdale et al. (2019), dietary changes are empirically linked to mental health symptom reduction; however, patients must be trained to track foods, choose correct part sizes, and provide guidance on eating properly with specific food mediations. Marx et al. (2017) similarly noted that, while dietary

supplementation and change can create positive effects, the changes must be consistent. Thus, the patient must be willing and capable of permanently incorporating changes into their lifestyle to see change over a gradual period.

Nutritional Therapies for Mental Disorders

This section will discuss specific disorders and the associated symptoms, biochemical responses and abnormalities, and vitamin supplementation responses. Each sub-section is devoted to a specific mental health disorder. First, major depressive disorder is reviewed in the following sub-section.

Major Depressive Disorder

Major depression is a mental disorder characterized by extreme anxiety, sadness, low mood, loss of interest in commonly pleasurable activities, and loss of appetite (Lakhan and Vieira, 2010). The most common medications used to treat depressive disorders include antidepressants (e.g., selective serotonin reuptake inhibitors) and psychotherapy. Various scholars have examined the fundamental causes of major depressive disorders (Kehr et al., 2018). Major depressive disorders are linked to a deficiency in critical neurotransmitters such as dopamine, serotonin, GABA, and noradrenaline. According to Kehr et al. (2018) reducing symptoms of major depressive disorders is critically linked to exploring specific foods and nutritional supplements that may relieve patients of persistent depressive symptoms, such as low moods. Because the absence of critical neurotransmitters is associated with major depression, supplementation of food rich in precursor nutrients of the neurotransmitters is noted to accelerate the replenishment of the deficient neurotransmitters and relieve patients of depressive symptoms. For instance, Lakhan and Vieira (2010) argued that foods rich in amino acids, tryptophan, methionine, phenylalanine, and tyrosine effectively reduce mood disorders. Tryptophan is a

nutrient that contains the direct building blocks for serotonin. Thus, consuming foods rich in tryptophan, such as salmon, prawns, eggs, and spinach, should facilitate the restoration of diminished serotonin levels in victims of depression.

Diminished dopamine levels are associated with low moods and depressive symptoms. Researchers have further illustrated that phenylalanine is a precursor of tyrosine, the direct precursor of dopamine (Kehr et al., 2018; Lakhan and Vieira, 2010; Olagunju et al., 2019). Generally, consuming foods or dietary supplements rich in phenylalanine leads to the production of dopamine in increased quantities. The specific foods that may be consumed to enhance dopamine levels include tea and coffee. Hence, the treatment of depression is achieved by consuming foods rich in phenylalanine and tyrosine (Olagunju et al., 2019).

A sum of six articles was found related to depression symptom treatment through diet or supplementation. Table 2 in Appendix D demonstrates these articles discussed in this section. First, Bjelland et al. (2009) assessed 5,918 patients in the Hordaland Health Study. Patients were male and female and ranged from 46-49 and 70-74. The patients' information was gathered regarding plasma choline concentrations and their depression and anxiety scales measured by the Hospital Anxiety and Depression Scale. Bjelland et al. found that the lower choline quintile was associated with higher anxiety. However, the authors did not find a relationship between choline concentration and depression.

A secondary model of depression treatment is the intake of Omega-3 fatty acids. Omega-3 fatty acids can be obtained through nutritional supplements or eating foods such as catfish, spinach, and shrimp. Godos et al. (2019) performed a review of the application of Omega-3 fatty acids to reduce depressive symptoms that elucidates the application of the nutritional treatment model. Firstly, Omega-3 fatty acids are referred to as polyunsaturated fats (PUFAs). These

include multiple acids, such as stearidonic acid, which contribute to the Omega-3 complex. Omega-3 is obtained from soybean, canola, walnut, flaxseed, chia, and hemp seeds. Intake of Omega-3 fatty acids leads to increased neurotransmitter regulation, modulation of adult hippocampal neurogenesis, and synaptogenesis. Through these processes, symptoms of depression are reduced with a daily intake of Omega-3 fatty acids. Similarly, Hallahan et al. (2016) and Deacon et al. (2017) performed an examination of Omega-3 for treatment of symptoms of depression and found results similar to those of Godos et al. (2019). Overall, the use of Omega-3 is considered an ideal treatment model for reducing the symptoms of depression.

In another study, Ganança et al. (2017) explored the relationship between Omega-3 polyunsaturated fatty acid supplementation and symptoms of depression. The authors gathered a sample of 16 patients with symptomatic major depressive disorder. The patients were tested for plasma phospholipid levels of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). Ganança et al. reported that five patients showed decreased depression because of consuming Omega-3 Fatty acids. The author's findings were limited, as they indicated the need for replication with larger sample size. Further, the authors did not explore depression severity. Rondanelli et al. (2011) assessed the treatment of Omega-3 Fatty acids for elderly depression. The authors employed an intervention style design that included 46 females with depression aged 66-95. The intervention group received 2.5 g/day of n-3 LCPUFA, with 1.67 grams of EPA and 0.83 grams of DHA. A separate group of 24 placebo patients was included. The findings indicated that Omega-3 Fatty acids reduced depressive symptoms and improved quality of life as determined through the Geriatric Depression Scale (GDS), which illustrated a significant decrease in scales after the introduction of LCPUFA (95% CI, -3.2 [-5.9, -0.6]).

In addition, researchers have linked specific nutritional deficiencies to symptoms of depression and other mental health disorders. These include a lack of minerals, vitamins, Omega-3 fatty acids, and amino acids. For example, Ganança et al. (2017) noted the possible link between supplemental nutrition and reduced depression symptoms. Participants were recruited from the New York State Psychiatric Institutional Review Board for the authors' study. Patients who were diagnosed with symptoms of major depression disorder were included in the study. A total of 14 participants were provided Omega-4 Polyunsaturated Fatty acids (PUFA) supplementation. Only one of the 14 patients was taking medication for their depression during the study trial. Resultantly, the authors noted that the consumption of two grams of Omega-3 fatty acids is effective for depression reduction when taken each day. For patients that demonstrated a high risk of suicidal ideation, 9.6 grams was effective for reducing symptoms of depression. Specifically, the patients experienced a 50% decrease of depression as rated through the Hamilton Depression Rating Score examination (17.1±3.7 at baseline to 12.3 ± 6.0 at study endpoint (t=3.137, df=15, p=0.007).

Bae and Kim (2018) provided a systematic review regarding Omega-3 Fatty acids in elderly patients with symptoms of depression. The authors reviewed the literature and identified six studies that included a sum of 4,605 patients. The findings indicated that Omega-3 fatty acid was relatively effective in treating depression. The authors, however, cautioned that these findings were only relevant to patients with mild or moderate depression.

Berridge (2017) assessed the role of vitamin D and depression symptoms by focusing on regulatory and cellular mechanisms. The authors found that some chemical evidence indicates that vitamin D is useful to reduce the brain's imbalance. Berridge provided a useful review for understanding the mechanics that may influence the impact of vitamin D on depression

symptoms. Vitamin D was also useful for psychiatric disorders through the systematic review conducted by Jamilian et al. (2019). The authors used the Cochrane risk of bias tool and pooled the meta-analysis findings. The findings indicated a significant reduction in depression symptoms through supplementation with vitamin D. Also, Jamilian et al. provided a review of vitamin D upon patients with psychiatric disorders. The authors reviewed six databases and pooled the findings, demonstrating positive statistical evidence for the use of vitamin D to deal with depression symptoms [weighted mean difference (WMD): -3.91; 95% CI: -5.15 -2.66), I^2= 85.9%].

In terms of depression symptoms and nutrition, Khanna et al. (2019) reviewed 1000 articles from 1978 to 2017. The relevant 56 articles indicated that nutrition played a key role in reducing depression symptoms in adolescents. The authors noted the need for continued empirical evidence for illustrating the impact between nutrition and depression symptoms. Reduction of depression symptoms was also possible through probiotic treatment through McEwan and Fenasse's (2019) review of the literature regarding the gut-axis biome and treatment through probiotics. However, the authors' limitation was the lack of a clear systemic review structure.

Young et al. (2019) performed a systematic and meta-analysis of the literature and identified a risk of placebo effect for overall mood among individuals with depression. The authors also noted that vitamin B did reduce stress but did not show significant results in reducing depression symptoms. Young et al. argued that vitamin B may be limited to aid individuals with poor nutrition and increased stress, but not vernal anxiety disorder. Mickkelsen et al. (2017) also reviewed the impact of vitamin B on depression symptoms and noted that the treatment impacts cytokine networks, which may influence the manifestation of depression symptoms. However, the

authors noted a greater need to explore empirical literature that links the immune cell changes in depressed patients with vitamin B treatment.

De Koning et al. (2016) explored the role of B12 and folic acid supplementation on depressive symptomology. The authors explored lowering elevated plasma homocysteine (Hcy) concentrations through vitamin B12 and folic acid treatment. A total of 2,919 participants over the age of 65 were provided 500 µg vitamin B_{12} and 400 µg folic acid daily or a placebo for two years. De Koning et al. reported 2-year changes through ANCOVA analysis. The findings indicated that B12 and folic acid supplementation created a small effect on elevated plasma homocysteine (Hcy) levels but did not impact depressive symptoms.

Föcker et al. (2018) explored the influence of vitamin D on symptoms of depression in child and adolescent psychiatric patients. The authors used a randomized controlled trial that enrolled 200 patients. The enrolled children held vitamin D deficiencies and a mild depression diagnosis. The patients received 2,640 International United (IE) vitamin D3 once a day for 28 days. They also reported that vitamin B supplementation positively impacted adolescents and children. However, the authors also noted that the findings should also be replicated in health (e.g., non-deficient) populations to fully study the effect.

Generalized Anxiety Disorder

Generalized anxiety disorder is characterized by persistent worry, fear, and/or stress in an individual's daily life. Anxiety can include constant fatigue, difficulty concentrating, irritability, muscle tension, and restlessness (NIMH, 2019). According to the Anxiety and Depression Association of America (ADAA, 2019), a total of 40 million adults are impacted by anxiety disorders in the United States. General anxiety is treatable with medication; however, only 36% of the population seeks treatment (ADAA, 2019). Resultantly, the increased risk of general

anxiety in the United States has prompted multiple examinations for treatment alternatives for patients suffering from anxiety symptoms (Lakhan & Vieira, 2010).

In sum, general anxiety is illustrated to be reduced by combinations of herbal and dietary supplementation (Saeed et al., 2007). Some empirical evidence exists for the intake of Omega-3 fatty acids and 5-hydroxytryptophan (Saeed et al., 2017). Additionally, choline, reduction of gluten, and Omega-3 are effective in reducing some symptoms of an anxiety disorder (Bjelland et al., 2009; Messaoudi et al., 2011; Ramsey, 2017; Saeed et al., 2007). There is a gap in the current literature; however, that demonstrates the specific nutrients that are empirically tested for anxiety reduction. Further, there appears to be a lack of consensus on the proper dosage and ideal supplementation for those suffering from an anxiety disorder. In the following section, the researcher presents the conclusion of this literature review and provides a brief overview of the most salient topics.

A total of three articles were found related to the use of nutrition or supplementation for anxiety-related mental illness. Table 4 in Appendix F demonstrates these findings. First, Ari et al. (2017) explored the impact of exogenous ketone supplementation on treating anxiety-related behavior. For this purpose, the sample included rats fed chronically for 83 days and administered exogenous ketones sub-chronically for seven days. The outcomes were measured through exploring anxiety measures on an elevated plus-maze. The findings were assessed through a blinded observer and video tracking system to measure blood and glucose levels. The authors found that chronic and sub-chronic ketone supplementation increased blood and glucose levels and decreased anxiety-related behavior. Further, the authors noted that these findings should be ideally replicated through human trials.

One alternative treatment model for anxiety is herbal supplements for decreasing anxiety symptoms. Saeed et al. (2007) provided a foundational examination of the dietary and herbal links to reduced general anxiety. The authors provided a systematic review of the literature regarding supplements used to treat anxiety. This included dietary remedies, herbal supplements, and neurotransmitter and hormonal precursors. The most common models for treating general anxiety were Kava, St. John's Wort, Passionflower, Cannabis, Inositol, Omega-3 fatty acids, and the neurotransmitter precursors 5-hydroxytryptophan. The authors argued that patients with general anxiety were likely to self-medicate with these supplements without consultation with a doctor. The authors urged individuals to reach out to a medical professional first to ensure that the products used were appropriate. However, the authors did note that empirical evidence was provided for the use of Omega-3 fatty acids and 5-hydroxytryptophan to treat anxiety. According to the authors, further research is needed to understand how these supplements operate to relieve anxiety symptoms.

Researchers also illustrated that symptoms of fear and panic from generalized anxiety disorder are reduced with herbal supplementation. Ari et al. (2017) examined reducing anxiety-related behavior, such as panic and fear, using exogenous ketone supplementation. Ketone supplements are molecules that can reduce carbohydrates and increase protein. Through supplementation, the liver converts fat into ketones used as fuel. For the sample, the authors used a series of rats provided food enriched with exogenous ketone supplements for 83 days. Anxiety measures were assessed using an elevated plus maze, which is considered a model of assessing anxiety in rat samples. The authors reported that chronic and sub-chronic exogenous ketone supplementation reduced anxiety and may be applicable for human trials. Ketone supplementation has not been tested on human samples for anxiety reduction. Further empirical

examinations are needed to support the claims of Kovacs et al. (2017) to demonstrate statistical evidence of anxiety symptom reduction resulting from herbal supplementation.

Kiecolt-Glaser et al. (2011) assessed Omega-3 supplementation to reduce general anxiety within a sample of medical students. The authors employed a randomized controlled trial with 68 medical students. The students were subjected to blood samples and blood pressure exams before and after the academic examinations. The students were also provided either a placebo or an Omega-3 supplement. The study's findings indicated that patients who were provided the Omega-3 supplementation found a significant reduction in anxiety symptomology. However, the authors' findings were limited by a lack of discussion regarding how external or internal factors, such as age, health status, and gender, may impact the response to Omega-3 among the trial patients. A limitation of the research regarding whole food and nutritional supplementations and specific to mental health disorders was a focus toward generalized anxiety disorder. A lack of research was identified in terms of panic disorders, phobias, and obsessive-compulsive disorders. Thus, indicating potential gaps in the research that may require researchers to further understand mental health disorders beyond generalized anxiety disorders in terms of the supplementations whole food approaches to potentially reduce negative symptomology.

Bipolar Disorders

For general bipolar disorders, Olagunju et al. (2019) provided a systemic review of clinical trials and articles from 2018 to 2019. Eligible reports included in Olaganuju et al.'s (2019) systematic review illustrated that nutrition, herbal supplementation, and nutritional deficiencies are potential contributors to adverse symptomology of general bipolar disorders. However, the authors noted that the findings point towards limitations in small sample size and

lack of empirical corroboration of findings. The findings are critical as the authors discussed the need to focus on larger sample sizes to corroborate the reviewed authors' findings.

Bipolar disorders include symptoms of major and reoccurring depressive episodes; however, mania is a key factor that separates bipolar disorder from major depression (Olagunju et al., 2019). Bipolar I refers to individuals that experience manic symptoms that may last seven or more days. Manic symptoms, associated with Bipolar I, may require hospital care due to significant depressive episodes (Olagunju et al., 2019). Bipolar II, refers to individuals that will cycle between high or low manias over periods of time. Converse to Bipolar I, individuals Bipolar II, do not experience the significant up cycle of mania that individuals with bipolar one experience. Finally, Cyclothymic Disorder is a mood disorder that is characterized by symptoms of significant ups and downs (Olagunju et al., 2019). Individuals may experience mood swings or depression dependent upon their specific diagnosis and symptoms (Olagunju et al., 2019). Patients with general bipolar disorder tend to produce a lot of vanadium, resulting in manic behavior that can include alternating periods of extreme happiness and extreme indifference or depression. Resultantly, patients with general bipolar disorder are treated with alternating psychotropic medication, such as lithium. However, the symptoms of bipolar disorder are challenging for patients to manage in everyday life (Hibar et al., 2018; Olagunju et al., 2019; Stahl et al., 2019).

Researchers have linked general bipolar disorder to biochemical abnormalities such as excess vanadium, vitamin B deficiency, and acetylcholine sensitivity. Firstly, vitamin B has been linked to reducing bipolar symptoms (such as anxiety, depression, and manic-cycles) in trial-based assessments. Jonsson (2018) performed a clinical assessment of vitamin supplementation for patients with bipolar type II disorder. The researcher examined the application of 20mg of

vitamin B3 for patients diagnosed with general bipolar disorder. They also examined the application of Nicotinic Acid (NA), a form of vitamin B3. The author reported that patients prescribed NA experienced a strong reduction of symptoms. After prolonged application of NA, patients could discontinue psychotropic medications for general bipolar disorder. After stopping NA, however, anxiety and depressive episodes reoccurred after 2 to 3 days. Jonsson, along with multiple other researchers (see Ozdogan et al., 2020; Petrov et al., 2017; Petrov et al., 2018), recommended the application of vitamin B to reduce bipolar symptoms such as manic swings, depression, and anxiety.

Omega-3 can treat general bipolar disorder by reducing symptoms of anxiety and agitation. For example, Amini et al. (2020) reported that the brain requires an adequate supply of Omega-3 oil to transmit signals for proper thinking, emotions, and moods. Similarly, Olagunju et al. (2019) found that patients with general bipolar disorder were frequently low in Omega-3 supplementation. Thus, the increased intake of Omega-3 oil was critical for reducing symptoms by treating the existing deficiency. Saunders et al. (2016) similarly noted that the treatment of Omega-3 and Omega-6 can be critical to reducing bipolar disorder symptoms. The author's assessed biomarkers and treatment studies to provide validation for the treatment of the disorder through nutritional supplementation. Resultantly, the authors identified five open-label trials that found Omega-3 intake as an effective treatment for depression and bipolar disorder symptoms. Saunders et al. emphasized the application of Omega-3 and 6 to decrease general bipolar disorder due to the metabolism into the PUFA biomarker.

Schizophrenia

Schizophrenia is a mental health condition that impacts an individual's perception of reality (Meehl, 2017). Typically, individuals with schizophrenia exhibit hallucinations, speech

impairment, delusion, and paranoia (Meehl, 2017). Schizophrenia can impact individuals lives differently based upon specific symptoms, age, medication, and context, such as support and family caregivers. Individuals that experience schizophrenic symptoms may lead well-adjusted lives if properly supported, medicated, and provided guidance regarding how to overcome adverse symptoms, such as speech impairments, paranoia, and hallucinations (Meehl, 2017). However, for some, schizophrenia can negatively impact an individual's ability to work, interact with others, and lead a normal day to day life (Meehl, 2017). Negative symptoms of schizophrenia can potentially include inability to socially interact, work a full- or part-time job, and gain educational opportunities that allow for social and financial mobility (Meehl, 2017).

Several scholars have associated the initial presentation of schizophrenia symptoms, particularly during the adolescence stage, with disruptions in the metabolism of amino acids (Khanna et al., 2019; Meehl, 2017; Olagunju et al., 2019). Disruption in the metabolism of amino acids prevents the successful production of serotonin (Khanna et al., 2019; Meehl, 2017; Olagunju et al., 2019). Previous research regarding schizophrenia has largely focused on potential medication that can ideally reduce symptomology of the mental disorder and create positive effects for the individual. Ideally, with appropriate support and medication, the individuals provide the opportunity to work, study, and interact with their peers, friends, and family (Khanna et al., 2019; Meehl, 2017; Olagunju et al., 2019). However, research regarding schizophrenia is less commonly researched when compared to the use of whole foods or nutritional supplements to reduce the adverse schizophrenic symptoms when compared to disorders such as depression or generalized anxiety disorder.

Overall, there is a lack of research examining nutritional supplement efficacy to reduce symptoms of schizophrenia. Omega-3 fatty acids (Mazza et al., 2019; Xu et al., 2019) and

Glycine (Greenwood et al., 2018; Imtiaz et al., 2018) are two nutritional supplements that are linked with positive reduction of symptoms. Conversely, Smesny et al. (2014) also explored Omega-3 Fatty acids in a sample of 81 patients. The authors explored the impact on psychosis after a 1-year assessment. The authors reported that Omega-3 Fatty acids decreased psychosis by normalizing the intercellular activity of patients and noted further need to explore the impact of Omega-3 Fatty acids on cellular activity. Ideally, future studies will be conducted to examine and categorize other food types and whether they could be effective in treating schizophrenia.

Two articles were found related to diet or nutritional health concerning schizophrenia. Table 3 in Appendix E demonstrates these results. Schizophrenia symptoms are also reduced through the application of glycine. Researchers have found that glycine reduces the symptoms of schizophrenia, such as hallucinations, emotional flatness, and social withdrawal. In a randomized controlled trial, Imtiaz et al. (2018) revealed that a dose of approximately 30 grams of glycine reduced the most adamant symptoms of schizophrenia that do not readily respond to commercially available medications. Similarly, Greenwood et al. (2018) noted that the effect of glycine is ideal for reducing auditory mismatch symptoms experienced by patients with schizophrenia. However, there is a need for increased empirical research regarding how glycine works to reduce schizophrenia symptoms.

More recent studies have established strong associations between Omega 3 fatty acids and reduced symptoms of schizophrenia. Mazza et al. (YEAR) assessed Omega-3 fatty acids and their role in reducing the symptoms of schizophrenia. The authors noted that the induction of Omega-3 fatty acids is useful for reducing agitation or the risk of psychotic episodes. The individual is unable to experience derealization and risk of suicidal harm. Further, these acids are

critical for developing and regulating cognitive functions, which may be critical for schizophrenia symptom reduction in adolescents.

Similarly, Zu et al. (2016) performed a controlled trial to assess the empirical evidence for using Omega-3 fatty acids to treat schizophrenia symptoms. The authors used a sample of 80 patients with schizophrenia that were split into two groups to receive either Omega-3 fatty acid or a placebo treatment. The authors found a significant correlation between Omega-3 fatty acid intake and reduced triglycerides. Reduction of triglycerides was associated with reduced agitation amongst patients with schizophrenia. Thus, the researchers indicated that Omega-3 fatty acids might be one treatment model for reducing schizophrenic symptoms.

Holloway (2016) assessed the role of herbal supplementation among schizophrenia and schizoaffective symptoms. The authors reviewed relevant literature and found a reduction of 33% of psychotic symptoms as reported among individuals suffering from schizophrenia that were supplemented with Omega-3 Fatty acids, Curcumin, Folic Acid, vitamin B12, vitamin B6, vitamin D, N-acetylcysteine, SAM-e, Bacopa Monniera, Ginkgo Biloba, Iron, Glycine, Stepholidine, Yokukansan, Orengadoku, and Ficus platyphylla. Again, the author's review was limited by a restricted discussion of the search strategy employed, which makes replication difficult for future assessments. Overall, the findings support the implementation of supplementation for schizophrenia, gained through whole foods or nutritional supplements, as a means of supporting reduced symptomology of depression and psychosis among individuals suffering from schizophrenia.

Studies Presenting a Variety of Mental Health Disorders

For studies that considered multiple disorders in a singular study, 13 articles were identified. Table 5 in Appendix G illustrates these results. Amongst these studies, a range of

disorders was examined by van de Rest et al. (2008) through reviewing outcomes of fish supplementation on mental health disorders. Fish-supplementation was also assessed by van de Rest et al. (2008) in a sample of 302 patients with psychiatric disorders ranging from depression to anxiety. The authors found that fish oil supplementation after 26 weeks did not reduce the patients' mental wellbeing scores. The findings indicated the need for further exploration due to the lack of congruity in acid treatment for mental disorders.

Firth et al. (2018) provided a review of nutritional deficiencies and psychosis through a review of electronic databases. The authors identified 28 relevant studies that explored vitamin and mineral deficiencies alongside control patients. The findings indicated that vitamin D and folate's nutritional deficiencies were correlated with negative schizophrenia symptoms, such as psychosis and agitation. The authors noted the need for further studies that consider external and internal variables, such as the age, gender, ethnicity, and possible comorbidities of the patients.

Teasdale et al. (2019) explored six databases and assessed the impact of diet on severe mental illnesses, such as depression and bipolar I and II. The 58 discovered studies indicated that higher dietary energy was more likely to be associated with reducing mental illness symptoms, such as depression and anxiety. Next, Allen et al. (2017) discussed the importance of the gut-biome interaction in a systematic review. However, the authors' study did not provide a clear review strategy, which was a limitation of their study.

Grønli et al. (2013) assessed the impact of zinc deficiency in terms of multiple psychiatric disorders. The psychiatric disorders included major depression disorder and schizophrenia or other forms of psychosis-related mental illness. The results showed that zinc deficiency was significantly correlated with the prevalence of mental disorders. A control group

of 882 individuals was also examined in comparison. The authors found that zinc deficiency was more prevalent in psychiatric disorders.

Patients diagnosed with major depressive disorder, or individuals that experience depression as a comorbidity of other mental health disorders (such as bipolar and schizophrenia patients) a lack of dopamine is associated with a disruption in dopamine secretion, which leads to imbalances in cognitive and emotional responses. Dopamine is linked to depressive disorders when an imbalance occurs (Condone et al., 2019). Condone et al. assessed dopamine transportation by examining patients diagnosed with major depression disorder. The authors noted that poor dopamine transport to critical regions of the brain was correlated with depressive episodes (Condone et al., 2019). In sum, dopamine is a critical neurotransmitter linked with mental health disorders (Condone et al., 2019; Grace, 2018; Ledermann & Martin-Solch, 2018).

In terms of general nutritional supplementation, Gariballa et al. (2006) performed a randomized, double-blind, placebo-controlled trial with 45 hospitalized patients who received either a normal diet or nutritional supplementation. The patients were hospitalized for differing reasons, but all experienced a form of mental illness such as depression or bipolar symptoms. The outcomes were measured at baseline, six weeks, and six months. The authors found that nutritional supplementation led to a statistically significant improvement among mental illness symptoms with the most significant effects after six months. Results for vitamin D also revealed some positive results for reduction in depression.

Grung et al. (2017) explored the link between vitamin D and perceived mental health of adolescents using multivariate analysis and a randomized, double-blind placebo control trial of 50 patients. The authors explored vitamin D supplementation through pre-and post-tests of perceived mental wellbeing. Resultantly, patients with vitamin D presented with higher

perceptions of mental wellbeing and performance in daily energy and motivation. The perceived mental wellbeing included reduced depressive symptoms and anxiety, which improved the patients' ability to function daily.

Imtiaz et al. (2018) demonstrated that glycine positively impacted memory change and dopamine among mice samples. The authors assessed glycine's impact for a sample of 30 albino mice. Both a treatment and control group were used. After two weeks of doses, light and dark activity tests were used alongside brain and blood sample tests to examine chemical changes in the mice after treatment changes. The authors illustrated that glycine significantly impacts serotonin, dopamine, memory, and behavioral changes, related to mental illness symptomology.

Yohn et al. (2017) also explored glycine in a sample of mice. The authors applied glycine concentrations to mice and observed their responses to the T-maze barriers. The authors found that glycine impacted the behavioral and motivational dysfunctions in mice. They also reported positive findings in reducing negative motivational symptoms, which illustrated that the mice were more likely to experience motivation and positive behavioral functions after treatment with glycine. The study, however, was not replicated in a human trial.

In terms of nutrition and mental disorders, Jacka et al. (2011) explored the role of diet and mental health across the Hordaland Health Study, including a sample of 5,730 men and women from 46 to 74 years of age. The authors found that when adjusting for age, education, income, consumption, and smoking, a healthy diet was inversely related to symptoms of major depression. Men with poor habits were more likely to exhibit symptoms of depression and anxiety, while a traditional healthy diet was associated with reduced depression and anxiety in both men and women.

Messaoudi et al. (2011) explored the psychological impact of probiotics on a sample of 25 patients. The author's assessed psychological distress and the perceived stress levels at baseline and follow-up. The authors found that probiotics significantly improved psychological distress in somatization, depression, and anger-hostility. However, the authors' findings were limited regarding their small sample size and lack of a control group.

Probiotics. Mohammadi et al. (2016) also explored the probiotic impact on 70 patients through a double-blind placebo-controlled study. The patients were assessed based on their prescription of either probiotic yogurt or a probiotic tablet. The third group received placebo probiotics. The findings were assessed using the general health questionnaire (GHQ) and depression anxiety and stress scale (DASS) scores. The authors found that after six weeks, the intervention group reported significantly improved scores for depression and anxiety. The authors found that probiotic capsules and yogurt were both beneficial. The study, however, was limited in terms of the small sample size.

For probiotic assessment, Papalini et al. (2019) also explored a sample of 58 healthy subjects in a randomized, double-blind placebo-controlled study for a 28-day intervention. The authors found that probiotics reduced stress and improved memory by impacting the frontal cortex. The authors indicated that these supplements might be key in reducing stress in healthy populations and individuals with mental illness.

Sudo et al. (2004) explored the role of postnatal microbial impact on mice's stress response. Postnatal microbes are passed on from the mother to the child in both human and mammalian samples. According to the authors, microbes can improve stress and mental health responses. The authors explored the ideology that the gut and brain axis may mitigate stress. They reviewed hypothalamic–pituitary–adrenal (HPA) stress reactions in germ-free, pathogen-

free, and gnotobiotic mice. The authors found that microbiota impacted mice's stress response. Specifically, germ-free mice reduced stress during early induction. The authors indicated that these findings illustrate possible positive outcomes for stress reduction in multiple populations. However, the authors' findings were limited in terms of their lack of application in human populations.

Conclusion

The literature presented in this chapter included five topics with 41 relevant empirical articles: (a) major depressive disorder, (b) generalized anxiety disorder, (c) bipolar disorders, (d) schizophrenia, (e) and general mental health disorders. The reviewed research illustrated a link between consumed nutrients and the regulation of the cognitive functions of the brain and body (Gómez-Pinilla, 2008; Lim & Kwak, 2019; Parra et al., 2018). Similarly, nutritional supplements, such as Omega-3 and vitamin D, are recommended to reduce symptoms of mental health disorders (Adan et al., 2019; Davidson et al., 2017; Petroaie et al., 2018; Sharma & Reddy, 2019). Dopamine was linked with mental health (Condone et al., 2019; Grace, 2018; Ledermann & Martin-Solch, 2018); however, the nutritional supplements needed to regulate dopamine are absent in academic research. Also, serotonin was crucial in reducing mental health disorders (Holloway, 2016; Henry, 2020; Herrera et al., 2017).

Further, supplements, such as probiotics and vitamin B, were suggested for increasing the regulation of serotonin levels (Herrera et al., 2017). Finally, the gut-brain axis was reviewed concerning mental health disorders. Significant research indicated a link between the gut and the brain in regulating mental health disorders (Clapp et al., 2017; Sandhu et al., 2017). However, a lack of clinical trials is present for humans to understand the ideal supplementation, besides probiotics (Clapp et al., 2017). In the final section, the researcher discussed nutritional therapies

for mental disorders. For bipolar disorder I and II, vitamin B and Omega-3 were effective (Saunders et al., 2016; Olagunju et al., 2019). Omega-3 and vitamin D were also found useful for reducing depression symptoms (Lakhan and Vieira, 2010; Kehr et al., 2018; Olagunju et al., 2019). For schizophrenia, research was limited; however, Omega-3 was again found effective for some symptom reduction (Mazza et al., 2019; Xu et al., 2019). Finally, anxiety reduction was correlated with Omega-3 fatty acids and 5-hydroxytryptophan (Saeed et al., 2017).

Overall, there is a lack of synthesis across previous literature examinations regarding nutrition and mental health disorders. In the reviewed literature, a gap was illustrated regarding the consensus of the ideal nutrition for treating mental health disorders. The findings are presented in Chapter Five concerning empirical literature and the recommendations for practice and policy considering the reviewed literature. The following chapter will also emphasize the interpretation of the findings and limitations of the current study.

Chapter IV: Discussion

Mental health symptomology and illness are issues that will affect approximately 46.4% of individuals in the United States in their lifetimes (NIMH, 2019). Individuals with mental health disorders are more likely to experience an increased risk of self-harm and suicide (NAMI, 2019; NIMH, 2019). In terms of social impact, mental health disorders can lead to reduced productivity and loss of economic profit among various fields (NAMI, 2019; NIMH, 2019). Economically, the mental health burden creates $193.2 billion in lost earnings in the United States each year (NAMI, 2019). From a global perspective, loss of productivity due to mental health disorders leads to a $1 trillion loss each year (NAMI, 2019; NIMH, 2019).

Previous examinations regarding mental health have focused largely on the incidence rate of mental illness, treatment factors, and external and internal factors that influence mental health (Adan et al., 2019; Davidson et al., 2017; Petroaie et al., 2018; Sharma & Reddy, 2019). Multiple variables may aid in treating mental illness, such as the use of prescribed pharmaceutical drugs (Petroaie et al., 2018). However, a secondary vein of research has also illustrated the possible effectiveness of nutrition supplementation and dietary changes in reducing symptoms of mental illness (Kate et al., 2017; Naidoo et al., 2018).

Despite evidence indicating that dietary changes and nutrition may positively impact mental illness symptoms, there remains a need to provide a comprehensive review regarding the connection between diet and mental illness. As a result, the purpose of this study was to explore the current state of the literature that discusses the impact of diet and nutrition upon mental illness symptomology. The research question that guided this study was as follows: What is the effect of nutrition on individuals' mental health in the United States? The systemic review aimed to explore, synthesize, and present the available literature regarding the effect of nutrition on

individuals' mental health in the United States. The findings of the systematic review illustrated 547 eligible items for review. A total of 41 final articles aligned with the search criteria. The final topics demonstrated through the review of the literature included (a) major depressive disorder, (b) generalized anxiety disorder, (c) bipolar disorder, (d) schizophrenia, (e) and general disorders. In this chapter, the researcher aims to interpret the findings, present recommendations for study and practice, and discuss the limitations of this study. The following section presents the interpretation of findings concerning the literature presented in Chapter Four.

Interpretation of the Findings

Empirical Literature

In terms of empirical evidence, researchers have indicated that diet and supplementation might impact depressive symptomology (Bjelland et al., 219). For example, Omega-3 Fatty acids were effective in elderly patient samples (Ganança et al., 2017; Rondanelli et al., 2011). However, there is a need to expand these findings beyond the elderly patient sample used by previous researchers. The findings regarding vitamin D and vitamin B indicated positive results for deficient patients. These findings were limited by the bias that patients were previously deficient in the treated supplementation.

For patients with schizophrenia, the empirical literature indicated a positive impact through glycine (Greenwood et al., 2018) and Omega-3 Fatty acids (Kehr et al., 2018; Pawelczyk et al., 2015). The limitations of these studies were small sample sizes, a focus towards only two nutritional supplementations, and the exclusion of dietary impacts if any. In terms of stress, research regarding the role of nutrition and supplementation was found to be impactful in terms of Omega-3 fatty acid supplementation's significant reduction on stress (Kiecolt-Glaser et al., 2011). The remaining two studies identified used mice samples and did not explore human diet

or nutrition; however, the authors indicated the importance of the microbiota (Neufeld et al., 2011) and exogenous ketones (Ari et al., 2017).

Diet was also positively correlated with reducing depression (Jacka et al., 2011) in a large sample set. Amini et al. (2020) indicated positive Omega-3 fatty acids and depression results. Similar positive findings were reflected for fatty acids and Omega-3 (Smesny et al., 2014). However, the sample of 302 patients in the study by van de Rest et al. (2008) did not experience a significant reduction in depression and anxiety symptoms. For nutritional supplementation, Grønli et al. (2013) indicated that zinc was more commonly absent in psychiatric patients than in a control sample. Gariballa et al. (2016) also demonstrated positive impacts for nutritional supplementation, while Grung et al. (2017) illustrated the impact of vitamin D on improving mental health and wellbeing. Glycine was also useful in mice samples (Imtiaz et al., 2018; Yohn et al., 2017) to improve behavioral and motor dysfunctions and increase memory and behavioral changes. However, these findings limit the understanding in application to human samples. Probiotics were also found to reduce somatization, anger, depression symptoms (Mohammadi et al., 2016), and stress level reduction (Messaoudi et al., 2011; Papalini et al., 2019). In mice samples, the microbiota is also connected to reducing stress, which indicates useful results for mental health symptomology reduction (Sudo et al., 2004). These studies, however, were limited by small sample sizes.

Limitations and Bias in the Research

The most noticeable biases in the reviewed articles were present in the systematic reviews relevant to the inclusion criteria. In the empirical literature, the designs used included randomized, double-blind placebo-controlled studies, controlled examinations in human and mice trials, cross-sectional analyses, blood sample and clinical data assessments using baseline

and intervention assessments, basal behavior comparisons in mice samples, multivariate analysis of secondary data, and intervention studies. The limitations noted in the empirical literature indicate that the use of mice samples limits the understanding of applying findings for human trials, which requires additional research. Further, due to the small sample sizes used in many of the studies, there is a need for continued corroboration and replication.

A critical limitation of the reviewed literature is a lack of focus specific to race. Previous assessments explored factors related to socio demographic and cultural characteristics that influence nutrition, supplementations, mental health outcomes for minorities across the United States (Dhillon et al., 2019; Jones et al., 2021). However, when exploring nutrition whole food supplement to aid in the reduction of mental health symptomology, there is an absence of understanding specific to variation between racial categories in the United States. Nutritional food access is characterized by significant disparities between sociocultural, demographic, and ethnic and racial groups in the United States. Thus, future researchers are suggested to examine this limitation to provide renewed information that will address this critical gap in the reviewed literature.

Limitations

The main limitation of this review was the methodology and design. The use of the systematic review approach was ideal for the purpose of the study to examine the relationship between whole food on mental health amongst adults. However, the presented findings are subject to generalization due to the various approaches, sample sizes, and methodologies used in the different studies included in this review. The implications of these limitations throughout this review demonstrate the findings and the different models used by each researcher. Further, the systematic review approach is not a method of collecting primary data, limiting the presentation

of a new finding. However, the purpose of providing a broad overview of nutrition and diet in terms of mental illness treatment is a new addition to the literature that may guide future researchers and practitioners.

Recommendations

Recommendations for Future Research

In this section, four key recommendations for future research are presented. These recommendations are based on the findings from the systematic review of the literature and include: 1. Sample Size; 2. Human Trials; 3. Focus on Dietary Impact; and 4. Focus on Specification of Nutritional Supplementation, 5. To include Diversity.

Sample Size

The first recommendation for future research is to increase the sample size. The study samples used in the empirical literature ranged from thousands to 20 or fewer participants. In small sample sizes, the transferability of the findings is limited. Further, it is unclear if the sample can provide a cohesive non-biased representation of the larger population. Ideally, future researchers will consider expanding previous studies with an increased sample size for better quantitative findings.

Human Trials

The second recommendation is to replicate mice and animal models in human trials. The majority of reviewed literature represented human trials and interventions. However, the assessments provided by animal models indicated new avenues of research that may elucidate intercellular interaction between diet and nutrition supplementation in the human body. Ideally, the expansion into human clinical trials will demonstrate how diet, supplementation, and microbiota interact to influence mental health in the human population.

Focus on Dietary Impact

The third recommendation is to explore dietary impact more significantly through empirical assessments. The majority of literature focused largely on specific supplementation, such as probiotics and Omega-3 fatty acids. These studies provided a foundational perspective regarding the relationship between diet, nutrition, and mental illness. However, there remains a gap in the empirical literature that considers the impact of whole food diets that can address some of the symptomologies of individuals with mental illness. Further, as many new whole food trends emerge in popular culture, empirical studies that demonstrate the impact, if any, from dietary changes on mental illness are critical for providing individuals with fact-driven research to guide their nutritional changes. It is recommended that empirical research regarding the impact on dietary changes with mental illness is continually conducted to ensure that consumers are supported with facts regarding how to best support and improve their mental illnesses.

Focus on Specification of Nutritional Supplementation

The final recommendation is to address the specific nutritional supplementation across various human trial studies in the empirical literature. The provided literature primarily focused on vitamin B, D, B12, probiotics, and Omega-3 Fatty acids. These studies suggested contradictory findings, however. The lack of congruence in these findings indicates the need to expand the focus on nutritional supplementation into larger samples to demonstrate empirical evidence. Next, the recommendation for practice is presented.

To Include Diversity

Reviewed literature lacked focus that differentiated between racial and ethnic groups. Future researchers are suggested to include diversity as a means of understanding how nutritional and whole food access, as a means of reducing mental health symptomology, may be lacking for

certain groups within the United States. Improving diversity inclusion and racial and ethnic differentiation in empirical studies can provide a renewed understanding of current inequality gaps and the potential interventions to improve these issues in the United States,

Recommendations for Practice

In this section, two key recommendations for future practice are presented. These recommendations are based on the findings from the systematic review of the literature and include: 1. Consideration of Nutritional Supplementation and Dietary Changes for Mental Health; and 2. Critical Focus on Patients Nutritionary Intake.

Consideration of Nutritional Supplementation and Dietary Changes for Mental Health

Based on the findings discussed in this study, there is a need for physicians and practitioners to consider nutritional supplementation to increase their clients' mental health. The empirical literature indicated the positive impacts of Omega-3 Fatty acids, Curcumin, Folic Acid, vitamin B12, vitamin B6, vitamin D, glycine, and probiotics to treat mental illness symptoms. In tandem with pharmaceutical drugs, dietary changes and nutritional supplementation may aid patients with some relief of mental illness symptomology.

In addition, physicians need to consider the patient's personal dietary and nutritional intake. The general understanding derived from empirical research is that a healthy diet can aid in the reduction of some depression and anxiety symptomology and may reduce symptoms of psychosis. As such, physicians are encouraged to review current literature and assess if the patient's dietary and nutritional supplementation is met to ensure their path to wellbeing.

Implications

The findings of this study indicate a need for increased sample size and controlled studies in human populations to increase the understanding of how these factors interact with brain

function. This study implies that nutrition and diet can decrease some symptomology. Still, the lack of repeated trials and corroboration of findings in nutritional supplementation, such as zinc, is lacking. Further, there is a lack of studies that consider the impact, if at all, of whole food dietary changes on mental health. Future research must examine the implications of nutritional supplements and whole food dietary changes to better understand its impact on mental health. Additional research in this area is necessary to inform organizations, facilities, and institutions that provide meals to special populations to determine how to best care for their members, students, employees, etc. For example, public school cafeterias can use additional research in this area to inform the creation of their dietary menus for students. Changes in the dietary offerings within a school environment can significantly affect students' mental health and wellbeing. Research in this area can improve the mental health of these students by making whole-food changes in their menus, possibly improving student performance and achievement. Larger organizations that offer meals to their employees can also make meaningful changes in the dietary offerings to improve employee wellbeing and job performance. It is also possible that health-oriented changes at an organizational level can improve employee satisfaction, retention, and commitment to an organization given the care employers would have for their employees' wellbeing. Based on the findings of this review, it is evident that diet is associated with one's mental health and wellbeing. As such, findings from this study should be used to implement meaningful changes to improve mental health tangibly and sustainably. While this study and previous research have indicated that dietary changes in whole food can provide needed supplementation to improve mental health, more research is needed to understand how to best implement these changes.

Conclusion

The current systematic review indicates a need for randomized controlled trials. There is a lack of consideration for repeated trials and corroboration of findings in nutritional supplementation among human trials in the current literature. There is a critical need to consider the impact, if at all, of whole food dietary changes on mental health. Ideally, future researchers will consider replicating the reviewed studies to further describe how nutrition and diet may influence the reduction of mental illness symptomology.

References

Acharya, T., & Agius, M. (2017). The importance of hope against other factors in the recovery of mental illness. *Psychiatria Danubina*, *29*(3), 619-622. http://www.psychiatria-danubina.com/UserDocsImages/pdf/dnb_vol29_noSuppl%203/dnb_vol29_noSuppl%203_619.pdf

Adan, R. A., van der Beek, E. M., Buitelaar, J. K., Cryan, J. F., Hebebrand, J., Higgs, S., Schellekens, H., & Dickson, S. L. (2019). Nutritional psychiatry: Towards improving mental health by what you eat. *European Neuropsychopharmacology*, *29*(12), 1321-1332. https://doi.org/10.1016/j.euroneuro.2019.10.011

Afulani, P. A., Coleman-Jensen, A., & Herman, D. (2018). Food insecurity, mental health, and use of mental health services among nonelderly adults in the United States. *Journal of Hunger & Environmental Nutrition*, *15*(1), 29-50. https://doi.org/10.1080/19320248.2018.1537868

Aggarwal, A., Rehm, C. D., Monsivais, P., & Drewnowski, A. (2016). Importance of taste, nutrition, cost and convenience in relation to diet quality: Evidence of nutrition resilience among US adults using National Health and Nutrition Examination Survey (NHANES) 2007–2010. *Preventative Medicine*, *90*, 184-192. https://doi.org/10.1016/j.ypmed.2016.06.030

Allen, A. P., Dinan, T. G., Clarke, G., & Cryan, J. F. (2017). Psychology of the humanbrain-gutt–microbiome axis. *Social and Personality Psychology Compass*, *11*(4), e12309. https://doi.org/10.1111/spc3.12309

Amini, M., Bahmani, F., Foroozanfard, F., Vahedpoor, Z., Ghaderi, A., Taghizadeh, M., Karbassizadeh, H., & Asemi, Z. (2020). The effects of fish oil Omega-3 fatty acid supplementation on mental health parameters and metabolic status of patients with polycystic ovary syndrome: A randomized, double-blind, placebo-controlled trial. *Journal of Psychosomatic Obstetrics & Gynecology*, 1-9. https://doi.org/10.1080/0167482X.2018.150828

Ari, C., Kovács, Z., Juhasz, G., Murdun, C., Goldhagen, C. R., Koutnik, A.P., Poff, A. M., Kesl, S. L., & D'Agostino, D. P. (2017). Exogenous ketone supplements reduce anxiety-related behavior in Sprague-Dawley and Wistar Albino Glaxo/Rijswijk rats. *Frontiers in Molecular Neuroscience*, *9*, 137. https://doi.org/10.3389/fnmol.2016.00137

Bae, J. H., & Kim, G. (2018). Systematic review and meta-analysis of Omega-3-Fatty acids in elderly patients with depression. *Nutrition Research*, *50*, 1-9. https://doi.org/10.1016/j.nutres.2017.10.013

Bahramy, P., Mohammed-Alizadeh-Charandabi, S., Ramezani-Nardin, F., & Mirghafourvand, M. (2020). Serum levels of vitamin D, calcium, magnesium, and copper, and their

relations with mental health and sexual function in pregnant Iranian adolescents. *Biological Trace Element Research*, *198*(2), 440-448.

Basharat, S., Smir Gilani, S., Mustafa Qamar, M., Basharat, A., & Basharat, N. (2019). Beneficial effects of zinc on reducing severity of depression. *Journal of Psychology and Clinical Psychiatry*, *10*(4), 135-139.

Baumeister, R. F., & Leary, M. R. (1997). Writing narrative literature reviews. *Review of General Psychology*, *1*(3), 311-320. https://doi.org/10.1037/1089-2680.1.3.311

Bem, D. J. (1995). Writing a review article for Psychological Bulletin. *Psychological Bulletin*, *118*(2), 172–177. https://doi.org/10.1037/0033-2909.118.2.172

Berridge, M. J. (2017). Vitamin D and depression: Cellular and regulatory mechanisms. *Pharmacological Reviews*, *69*(2), 80-92.

Bjelland, I., Tell, G. S., Vollset, S. E., Konstantinova, S., & Ueland, P. M. (2009). Choline in anxiety and depression: The Hordaland Health Study. *The American Journal of Clinical Nutrition*, *90*(4), 1056-1060.

Briguglio, M., Dell'Osso, B., Panzica, G., Malgaroli, A., Banfi, G., Zanaboni Dina, C., Galentino, R., & Porta, M. (2018). Dietary neurotransmitters: A narrative review on Current knowledge. *Nutrients*, *10*(5), 591. https://doi.org/10.3390/nu10050591

Caires, R., Sierra-Valdez, F. J., Millet, J. R. M., Herwig, J. D., Roan, E., Vásquez, V., & Cordero-Morales, J. F. (2017). Omega-3 fatty acids modulate TRPV4 function through plasma membrane remodeling. *Cell Reports*, *21*(1), 246-258. https://doi.org/10.1016/j.celrep.2017.09.029

Camfield, D., McIntyre, E., & Sarris, J. (2017). *Evidence-based herbal and nutritional treatments for anxiety in psychiatric disorders*. Springer.

Chelakkot, C., Ghim, J., & Ryu, S. H. (2018). Mechanisms regulating intestinal barrier integrity and its pathological implications. *Experimental & Molecular Medicine*, 50, 1-9. https://www.nature.com/articles/s12276-018-0126-x

Clapp, M., Aurora, N., Herrera, L., Bhatia, M., Wilen, E., & Wakefield, S. (2017). Gut microbiota's effect on mental health: The gut-brain axis. *Clinical Practice*, *7*(4), 131-136. https://doi.org/10.4081/cp.2017.987

Cockburn, N., Pradhan, A., Taking, M. W., Kisely, S., & Ford, P. J. (2017). Oral health impacts of medications used to treat mental illness. *Journal of Affective Disorders*, *223*, 184-193. https://doi.org/10.1016/j.jad.2017.07.037

Crowe, J., Lacy, C., & Columbus, Y. (2018). Barriers to food security and community stress in an urban food desert. *Urban Science*, *2*(2), 46.

De Koning, E. J., Van der Zwaluw, N. L., Van Wijngaarden, J. P., Sohl, E., Brouwer-Brolsma, E. M., Van Marwijk, H. W., Enneman, A. W., Swart, K. M. A., Van Dijk, S. C., Ham, A. C., Van der Velde, N., Uitterlinden, A. G., Penninx, B. W. J. H., Elders, P. J. M., Lips, P., Dhonukshe-Rutten, R. A. M., Van Schoor, N. M., & De Groot, L. C. (2016). Effects of two-year Vitamin B12 and folic acid supplementation on depressive symptoms and quality of life in older adults with elevated homocysteine concentrations: Additional results from the B-PROOF study, an RCT. *Nutrients*, *8*(11), 748.

Deacon, G., Kettle, C., Hayes, D., Dennis, C., & Tucci, J. (2017). Omega 3 polyunsaturated fatty acids and the treatment of depression. *Critical Reviews in Food Science and Nutrition*, *57*(1), 212-223. https://doi.org/10.1080/10408398.2013.876959

Demelash, S. (2017). The role of micronutrient for depressed patients. *Journal of Neurology and Neurorehabilitation*, *3*(2).

Dhillon, J., Diaz Rios, L. K., Aldaz, K. J., De La Cruz, N., Vu, E., Asad Asghar, S., ... & Ortiz, R. M. (2019). We don't have a lot of healthy options: Food environment perceptions of first-year, minority college students attending a food desert campus. *Nutrients*, *11*(4), 816.

Dinan, T. G., & Cryan, J. F. (2017). The microbiome-gut-brain axis in health and disease. *Gastroenterology Clinics*, *46*(1), 77-89. https://doi.org/10.1016/j.gtc.2016.09.007

Draper, C. E., Bosire, E., Prioreschi, A., Ware, L. J., Cohen, E., Lye, S. J., & Norris, S. A. (2019). Urban young women's preferences for intervention strategies to promote physical and mental health preconception: A Healthy Life Trajectories Initiative (HeLTI). *Preventative Medicine Reports*, *14*, 100846. https://doi.org/10.1016/j.pmedr.2019.100846

Eratte, D., Dowling, K., Barrow, C. J., & Adhikari, B. (2018). Recent advances in the microencapsulation of omega-3 oil and probiotic bacteria through complex coacervation: A review. *Trends in Food Science & Technology*, *71*, 121-131. https://doi.org/10.1016/j.tifs.2017.10.014

Firth, J., Carney, R., Stubbs, B., Teasdale, S. B., Vancampfort, D., Ward, P. B., Berk, M., & Sarris, J. (2018). Nutritional deficiencies and clinical correlates in first-episode psychosis: A systematic review and meta-analysis. *Schizophrenia Bulletin*, *44*(6), 1275-1292.

Föcker, M., Antel, J., Grasemann, C., Führer, D., Timmesfeld, N., Öztürk, D., Peters, T., Hinney, A., Hebebrand, J., & Libuda, L. (2018). Effect of a Vitamin D deficiency on depressive symptoms in child and adolescent psychiatric patients–a randomized controlled trial: Study protocol. *BMC psychiatry*, *18*(1), 57. https://link.springer.com/article/10.1186/s12888-018-1637-7

Foster, J. A., Rinaman, L., & Cryan, J. F. (2017). Stress & the gut-brain axis: Regulation by the microbiome. *Neurobiology of Stress*, *7*, 124-136. https://doi.org/10.1016/j.ynstr.2017.03.001

Ganança, L., Galfalvy, H. C., Oquendo, M. A., Hezghia, A., Cooper, T. B., Mann, J. J., & Sublette, M. E. (2017). Lipid correlates of antidepressant response to Omega-3 polyunsaturated fatty acid supplementation: A pilot study. *Prostaglandins, Leukotrienes and Essential Fatty Acids*, *119*, 38-44. https://doi.org/10.1016/j.plefa.2017.03.004

Gardner, C. (2018). Trade-offs in rigor and generalizability in a diet trial of glycemic control in adults with type 2 diabetes using whole foods and dietary supplements. *The American Journal of Clinical Nutrition*, *108*(2). https://doi.org/10.1093/ajcn/nqy172

Gariballa, S., Forster, S., Walters, S., & Powers, H. (2006). A randomized, double-blind, placebo-controlled trial of nutritional supplementation during acute illness. *The American Journal of Medicine*, *119*(8), 693-699. https://doi.org/10.1016/j.amjmed.2005.12.006

Gibson, E. L. (2018). *Tryptophan supplementation and serotonin function: Genetic variations in behavioural effects*. Cambridge University Press.

Godos, J., Ferri, R., Caraci, F., Cosentino, F. I. I., Castellano, S., Galvano, F., & Grosso, G. (2019). Adherence to the Mediterranean diet is associated with better sleep quality in Italian adults. *Nutrients*, *11*(5), 976. https://doi.org/10.3390/nu11050976

Golubeva, A. V., Crampton, S., Desbonnet, L., Edge, D., O'Sullivan, O., Lomasney, K. W., Zhdanov, A. V., Crispie, F., Moloney, R. D., Borre, Y. E., Cotter, P. D., Hyland, N. P., O'Halloran, K. D., Dinan, T. G., O'Keeffe, G. W., & Cryan, J. F. (2015). Prenatal stress-induced alterations in major physiological systems correlate with gut microbiota composition in adulthood. *Psychoneuroendocrinology*, *60*, 58-74. https://doi.org/10.1016/j.psyneuen.2015.06.002

Gómez-Pinilla, F. (2008). Brain foods: The effects of nutrients on brain function. *Nat Rev Neuroscience*, *9*(7), 568-578. https://doi.org/10.1038/nrn2421

Greenwood, L. M., Leung, S., Michie, P. T., Green, A., Nathan, P. J., Fitzgerald, P., Johnston, P., Solowij, N., Kulkarni, J., & Croft, R. J. (2018). The effects of glycine on auditory mismatch negativity in schizophrenia. *Schizophrenia Research*, *191*, 61-69. https://doi.org/10.1016/j.schres.2017.05.031

Grønli, O., Kvamme, J. M., Friborg, O., & Wynn, R. (2013). Zinc deficiency is common in several psychiatric disorders. *PloS one*, *8*(12), e82793. https://doi.org/10.1371/journal.pone.0082793

Gronroos, N. N. (2017). *Intake of Omega-3 polyunsaturated fatty acids and associations with cardiometabolic risk factors* [Doctoral dissertation, University of Minnesota].

https://www.proquest.com/docview/1968634894?pq-origsite=gscholar&fromopenview=true

Grung, B., Sandvik, A. M., Hjelle, K., Dahl, L., Frøyland, L., Nygård, I., & Hansen, A. L. (2017). Linking Vitamin D status, executive functioning and self-perceived mental health in adolescents through multivariate analysis: A randomized double-blind placebo control trial. *Scandinavian Journal of Psychology*, *58*(2), 123-130. https://doi.org/10.1111/sjop.12353

Hallahan, B., Ryan, T., Hibbeln, J. R., Murray, I. T., Glynn, S., Ramsden, C. E., SanGiovanni, J. P., & Davis, J. M. (2016). Efficacy of omega-3 highly unsaturated fatty acids in the treatment of depression. *British Journal of Psychiatry*, *209*(3), 192-201. https://doi.org/10.1192/bjp.bp.114.160242.

Henry, L. (2020). *Physical health, mental health, and nutrition. Experiences of Hunger and Food Insecurity in College*. Palgrave (pp. 61-78).

Herrera, A., Munoz, P., Steinbusch, H. W., & Segura-Aguilar, J. (2017). Are dopamine oxidation metabolites involved in the loss of dopaminergic neurons in the nigrostriatal system in Parkinson's disease? *ACS Chemical Neuroscience*, *8*(4), 702-711.

Hibar, D. P., Westlye, L. T., Doan, N. T., Jahanshad, N., Cheung, J. W., Ching, C. R. K., Versace, A., Bilderbeck, A. C., Uhlmann, A., Mwangi, B., Kramer, B., Overs, B., Hartberg, C. B., Abé, C., Dima, D., Grotegerd, D., Sprooten, E., Boen, E., Jimenez, E., Howells, F. M., … & Andreassen, O. A. (2018). Cortical abnormalities in bipolar disorder: An MRI analysis of 6503 individuals from the ENIGMA Bipolar Disorder Working Group. *Molecular Psychiatry*, 23, 932-942. https://doi.org/10.1038/mp.2017.73

Holloway, J. B. (2016). The role of herbal and nutraceutical supplementation in the amelioration of schizophrenia and schizoaffective symptomology. *Scientia et Humanitas*, *6*, 95-114.

Hunter, P. M., & Hegele, R. A. (2017). Functional foods and dietary supplements for the management of dyslipidaemia. *Nature Reviews Endocrinology*, 13, 278-288. https://doi.org/10.1038/nrendo.2016.210

Imtiaz, S., Ikram, H., Ayaz, M., Qadir, M. I., & Muhammad, S. A. (2018). Effect of glycine: Studying memory and behavioral changes in mice. *Pakistan Journal of Pharmaceutical Sciences*, *31*(5).

Jacka, F. N., Mykletun, A., Berk, M., Bjelland, I., & Tell, G. S. (2011). The association between habitual diet quality and the common mental disorders in community-dwelling adults: The Hordaland Health study. *Psychosomatic Medicine*, *73*(6), 483-490.

Jamilian, H., Amirani, E., Milajerdi, A., Kolahdooz, F., Mirzaei, H., Zaroudi, M., Ghaderi, A., & Asemi, Z. (2019). The effects of Vitamin D supplementation on mental health, and biomarkers of inflammation and oxidative stress in patients with psychiatric disorders: A

systematic review and meta-analysis of randomized controlled trials. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *94*, 109651. https://doi.org/10.1016/j.pnpbp.2019.109651

Jasarevic, E., Rodgers, A. B., & Bale, T. L. (2015). A novel role for maternal stress and microbial transmission in early life programming and neurodevelopment. *Neurobiology of Stress*, *1*, 81-88. https://doi.org/10.1016/j.ynstr.2014.10.005

Jonsson, B. H. (2018). Nicotinic acid long-term effectiveness in a patient with bipolar Type II disorder: A case of vitamin dependency. *Nutrients*, *10*(2), 134. https://doi.org/10.3390/nu10020134

Jones, R. E., Walton, T. N., Duluc-Silva, S., & Fly, J. M. (2021). Household Food Insecurity in an Urban Food Desert: A Descriptive Analysis of an African American Community. *Journal of Hunger & Environmental Nutrition*, 1-19.

Kehr, J., Yoshitake, T., Ichinose, F., Yoshitake, S., Kiss, B., Gyertyán, I., & Adham, N. (2018). Effects of cariprazine on extracellular levels of glutamate, GABA, dopamine, noradrenaline and serotonin in the medial prefrontal cortex in the rat phencyclidine model of schizophrenia studied by microdialysis and simultaneous recordings of locomotor activity. *Psychopharmacology*, 235, 1593-1607. https://doi.org/10.1007/s00213-018-4874-z

Khanna, P., Chattu, V. K., & Aeri, B. T. (2019). Nutritional aspects of depression in adolescents-A systematic review. *International Journal of Preventive Medicine*, *10*. https://dx.doi.org/10.4103%2Fijpvm.IJPVM_400_18

Kiecolt-Glaser, J. K., Belury, M. A., Andridge, R., Malarkey, W. B., & Glaser, R. (2011). Omega-3 supplementation lowers inflammation and anxiety in medical students: A randomized controlled trial. *Brain, Behavior, and Immunity*, *25*(8), 1725-1734. https://doi.org/10.1016/j.bbi.2011.07.229

Lacasse, J. R., & Leo, J. (2005). Serotonin and depression: A disconnect between the advertisements and the scientific literature. *Plos Medicine*, *2*(12), 392. https://doi.org/10.1371/journal.pmed.0020392

Lakhan, S. E., & Vieira, K. F. (2010). Nutritional and herbal supplements for anxiety and anxiety-related disorders: Systematic review. *Nutr J*., *9*(42), https://doi.org/ 10.1186/1475-2891-9-42

Ledermann, K., & Martin-Solch, C. (2018). Chronic pain, dopamine and depression: Insights from research on fibromyalgia. *Physiopathology and Treatment*. https://doi.org/ 10.5772/intechopen.82576

Li, S., Chen, K., Liu, C., Bi, J., He, Z., Luo, R., Yu, Y., & Wang, Z. (2017). Dietary diversity and mental health in preschoolers in rural China. *Public Health Nutrition*, *24*(7), 1869-1876. https://doi.org/ 10.1017/S1368980020003237

Lim, S. Y., & Kwak, Y. (2019). Effect of nutrients and exhaustive exercise on brain function. *Journal of Exercise Rehabilitation*, *15*(3), 341-345. https://doi.org/10.12965/jer.1938102.051

Marx, W., Isenring, E. A., & Lohning, A. E. (2017). Determination of the concentration of major active anti-emetic constituents within commercial ginger food products and dietary supplements. *European Journal of Integrative Medicine*, *10*, 19-24. https://doi.org/10.1016/j.eujim.2017.02.001

Mayer, E. A., Tillisch, K., & Gupta, A. (2015). Gut/brain axis and the microbiota. *The Journal of Clinical Investigation*, *125*(3), 926-938. https://doi.org/10.1172/JCI76304

McArdle, S. (2019). Parents' experiences of health services for the treatment of eating disorders: A qualitative study. *Journal of Mental Health*, *28*(4), 404-409. https://doi.org/10.1080/09638237.2017.1417558

McEwen, B., & Fenasse, R. (2019). Probiotics and depression: 'The link between the microbiome-gut-brain axis and digestive and mental health'. *Journal of the Australian Traditional-Medicine Society*, *25*(3), 127.

Messaoudi, M., Violle, N., Bisson, J. F., Desor, D., Javelot, H., & Rougeot, C. (2011). Beneficial psychological effects of a probiotic formulation (Lactobacillus helveticus R0052 and Bifidobacterium longum R0175) in healthy human volunteers. *Gut Microbes*, *2*(4), 256-261. https://doi.org/10.4161/gmic.2.4.16108

Mikkelsen, K., Stojanovska, L., Prakash, M., & Apostolopoulos, V. (2017). The effects of Vitamin B on the immune/cytokine network and their involvement in depression. *Maturitas*, *96*, 58-71. https://doi.org/10.1016/j.maturitas.2016.11.012

Mohammadi, A. A., Jazayeri, S., Khosravi-Darani, K., Solati, Z., Mohammadpour, N., Asemi, Z., Adab, Z., Djalali, M., Tehrani-Doost, M., Hosseini, M., & Eghtesadi, S. (2016). The effects of probiotics on mental health and hypothalamic–pituitary–adrenal axis: A randomized, double-blind, placebo-controlled trial in petrochemical workers. *Nutritional Neuroscience*, *19*(9), 387-395. https://doi.org/10.1179/1476830515Y.0000000023

Nair, K. P. (2020). Neurotransmitters and short-term effects of nutrition on behavior. In *Food and Human Responses* (pp. 45-63). https://doi.org/10.1007/978-3-030-35437-4_5

Neufeld, K. M., Kang, N., Bienenstock, J., & Foster, J. A. (2011). Reduced anxiety-like behavior and central neurochemical change in germ-free mice. *Neurogastroenterology & Motility*, *23*(3), 255-e119. https://doi.org/10.1111/j.1365-2982.2010.01620.x

Noseda, R., Borsook, D., & Burstein, R. (2017). Neuropeptides and neurotransmitters that modulate thalamo-cortical pathways relevant to migraine headache. *The Journal of Head and Face Pain*. https://doi.org/10.1111/head.13083

Olagunju, A., Gatchel, J. R., Morgan, J. A., Aftab, A., Chen, P. P., Dols, A., Sajatovic, M., & Regenold, W. T. (2019). Nutrition and bipolar disorders in older adults: A systematic review. *The American Journal of Geriatric Psychiatry*, *27*(3), S207-S208. https://doi.org/10.1016/j.jagp.2019.01.119

Opie, R. S., Itsiopoulos, C., Parletta, N., Sanchez-Villegas, A., Akbaraly, T. N., Ruusunen, A., & Jacka, F. N. (2017). Dietary recommendations for the prevention of depression. *Nutritional Neuroscience*, *20*(3), 161-171. https://doi.org/10.1179/1476830515Y.0000000043

Ordak, M., Matras, J., Muszynska, E., Nasieroswki, T., & Bujalska-Zadrozny, M. (2017). Magnesium in schizophrenia. *Pharmacological Reports*, *69*(5), 929-934. https://doi.org/10.1016/j.pharep.2017.03.022

Ozdogan, M. G., Aydin, E. F., Ustundag, M. F., Ceyhun, H. A., Oral, E., & Bakan, E. (2020). Homocysteine, chronotype and clinical course in bipolar disorder patients. *Nordic Journal of Psychiatry*, *74*(5), 340-345. https://doi.org/10.1080/08039488.2019.1710250

Papalini, S., Michels, F., Kohn, N., Wegman, J., Van Hemert, S., Roelofs, K., Arias-Vasquez, A., & Aarts, E. (2019). Stress matters: Randomized controlled trial on the effect of probiotics on neurocognition. *Neurobiology of Stress*, *10*, 100141. https://doi.org/10.1016/j.ynstr.2018.100141

Parra, G. A. M., Singh, R. H., Cetinyurek-Yavuz, A., Kuhn, M., & MacDonald, A. (2018). Status of nutrients important in brain function in phenylketonuria: A systematic review and meta-analysis. *Orphanet Journal of Rare Diseases*, 13. https://doi.org/10.1186/s13023-018-0839-x

Pawełczyk, T., Grancow, M., Kotlicka-Antczak, M., Trafalska, E., Gębski, P., Szemraj, J., Zurner, N., & Pawełczyk, A. (2015). Omega-3 Fatty acids in first-episode schizophrenia-a randomized controlled study of efficacy and relapse prevention (OFFER): Rationale, design, and methods. *BMC Psychiatry*, *15*(1), 97. https://link.springer.com/article/10.1186/s12888-015-0473-2

Petroaie, A. D., Cosmescu, A., Adorata, E., & Bolos, A. (2018). Dietary supplements and their influence on our mental health. *Bulletin of Integrative Psychiatry*, *24*(1). https://link.gale.com/apps/doc/A555806817/AONE?u=anon~1b234933&sid=googleScholar&xid=e9105cba

Petrov, V. A., Saltykova, I. V., Zhukova, I. A., Alifirova, V. M., Zhukova, N. G., Dorofeeva, Y. B., Tyakht, A. V., Kovarsky, B. A., Alekseev, D. G., Kostryukova, E. S., Mironova, Y. S., Izhboldina, O. P., Nikitina, M. A., Perevozchikova, T. V., Fait, E. A., Babenko, V. V.,

Vakhitova, M. T., Govorun, V. M., & Sazonov, A. E. (2017). Analysis of gut microbiota in patients with Parkinson's disease. *Bulletin of Experimental Biology and Medicine*, 162, 734-737. https://doi.org/10.1007/s10517-017-3700-7

Petrov, B., Aldoori, A., James, C., Yang, K., Algorta Perez, G., Lee, A., Zhang, L., Lin, T., Al Awadhi, R., Parquette, J. R., Samogyi, A., Eugene Arnold, L., Fristad, M. A., Gracious, B., & Ziouzenkova, O. (2018). Bipolar disorder in youth is associated with increased levels of vitamin D-binding protein. *Translational Psychiatry*, 8, 61. https://doi.org/10.1038/s41398-018-0109-7

Ramos-Lopez, O., Riezu-Boj, J. I., Milagro, F. I., & Martinez, J. A. (2018). Dopamine gene methylation patterns are associated with obesity markers and carbohydrate intake. *Brain and Behavior*, *8*(8). https://doi.org/10.1002/brb3.1017

Rieder, R., Wisniewski, P. J., Alderman, B. L., & Campbell, S. C. (2017). Microbes and mental health: A review. *Brain, Behavior, and Immunity*, 66, 9-17. https://doi.org/10.1016/j.bbi.2017.01.016

Rondanelli, M., Giacosa, A., Opizzi, A., Pelucchi, C., La Vecchia, C., Montorfano, G., Negroni, M., Berra, B., Politi, P., & Rizzo, A. M. (2011). Long chain Omega 3 polyunsaturated Fatty acids supplementation in the treatment of elderly depression: Effects on depressive symptoms, on phospholipids Fatty acids profile and health-related quality of life. *The Journal of Nutrition, Health & Aging*, *15*(1), 37-44.

Saeed, S. A., Bloch, R. M., & Antonacci, D. J. (2007). Herbal and dietary supplements for treatment of anxiety disorders. *American Family Physician*, *76*(4), 549-556.

Sandhu, K. V., Sherwin, E., Schellekens, H., Stanton, C., Dinan, T. G., & Cryan, J. F. (2017). Feeding the microbiota-gut-brain axis: diet, microbiome, and neuropsychiatry. *Translational Research*, *179*, 223-244. https://doi.org/10.1016/j.trsl.2016.10.002

Saunders, E. F. H., Ramsden, C. E., Sherazy, M. S., Gelenberg, A. J., Davis, J. M., & Rapoport, S. I. (2016). Omega-3 and Omega-6 polyunsaturated fatty acids in bipolar disorder: A review of biomarker and treatment studies. *The Journal of Clinical Psychiatry*. https://www.psychiatrist.com/jcp/bipolar/complementary/polyunsaturated-fatty-acids-in-bipolar-disorder/

Seyedi, M., Gholami, F., Samadi, M., Mahmoud, D., Affatpanah, M., Yekaninejan, M. S., Hashemi, R., Abdolah, M., Chamari, M., & Honarvar, N. M. (2019). The effect of vitamin D3 supplementation on serum BDNF, dopamine, and serotonin in children with attention-deficit/hyperactivity disorder. *CNS & Neurological Disorders - Drug Targets*, *18*(6), 496-501. https://doi.org/10.2174/1871527318666190703103709

Shariat, S., Hakimzadeh, V., & Pardakhty, A. (2020). The physicochemical and organoleptic evaluation of the nano/micro encapsulation of Omega-3 fatty acids in lipid vesicular systems. *Nanomedicine Journal*, *7*(1), 80-86. http://nmj.mums.ac.ir/article_14024.html

Sudo, N., Chida, Y., Aiba, Y., Sonoda, J., Oyama, N., Yu, X. N., Kubo, C., & Koga, Y. (2004). Postnatal microbial colonization programs the hypothalamic–pituitary–adrenal system for stress response in mice. *The Journal of Physiology*, *558*(1), 263-275. https://doi.org/10.1113/jphysiol.2004.063388

Slykerman, R. F., Hood, F., Wickens, K., Thompson, J. M. D., Barthow, C., Murphy, R., Kang, J., Rowden, J., Stone, P., Crane, J., Stanley, T., Abels, P., Purdie, G., Maude, R., Mitchell, E. A., & Probiotic in Pregnancy Study Group. (2017). Effect of Lactobacillus rhamnosus HN001 in pregnancy on postpartum symptoms of depression and anxiety: A randomised double-blind placebo-controlled trial. *EBioMedicine*, *24*, 159-165. https://doi.org/10.1016/j.ebiom.2017.09.013

Smesny, S., Milleit, B., Hipler, U. C., Milleit, C., Schäfer, M. R., Klier, C. M., Holub, M., Holzer, I., Berger, G. E., Otto, M., Nenadic, I., Berk, M., McGorry, P. D., Sauer, H., & Amminger, G. P. (2014). Omega-3 fatty acid supplementation changes intracellular phospholipase A 2 activity and membrane fatty acid profiles in individuals at ultra-high risk for psychosis. *Molecular Psychiatry*, *19*(3), 317-324. https://www.nature.com/articles/mp20137

Stahl, E. A., Breen, G., Forstner, A. J., McQuillin, A., Ripke, S., Trubetskoy, V., Mattheisen, M., Wang, Y., Coleman, J. R. I., Gaspar, H. A., de Leeuw, C. A., Steinberg, S., Whitehead Pavlides, J. M., Trzaskowski, M., Byrne, E. M., Pers, T. H., Holmans, P. A., Richards, A. L., Abbott, L., … & the Bipolar Disorder Working Group of the Psychiatric Genomics Consortium. (2019). Genome-wide association study identifies 30 loci associated with bipolar disorder. *Nature Genetics*, 51, 793-803. https://doi.org/10.1038/s41588-019-0397-8

Tarleton, E. K., Kennedy, A. G., Rose, G. L., Crocker, A., & Littenberg, B. (2019). The association between serum magnesium levels and depression in an adult primary care population. *Nutrients*, *11*(7), 1475. https://doi.org/10.3390/nu11071475

Teasdale, S. B., Ward, P. B., Samaras, K., Firth, J., Stubbs, B., Tripodi, E., & Burrows, T. L. (2019). Dietary intake of people with severe mental illness: Systematic review and meta-analysis. *The British Journal of Psychiatry*, *214*(5), 251-259

Testa, A., & Jackson, D. B. (2019). Food insecurity, food deserts, and waist-to-height ratio: variation by sex and race/ethnicity. *Journal of community health*, *44*(3), 444-450.

Theodorou, V. (2018). Probiotics, stress, and irritable bowel syndrome. *Phytothérapie*, *16*(6), 320-325. https://doi.org/10.3166/phyto-2018-0087

Tracy, S. J. (2019). *Qualitative research methods: Collecting evidence, crafting analysis, communicating impact*. John Wiley and Sons.

van de Rest, O., Geleijnse, J. M., Kok, F. J., van Staveren, W. A., Hoefnagels, W. H., Beekman, A. T., & de Groot, L. C. (2008). Effect of fish-oil supplementation on mental well-being

in older subjects: a randomized, double-blind, placebo-controlled trial. *The American Journal of Clinical Nutrition*, *88*(3), 706-713. https://doi.org/10.1093/ajcn/88.3.706

Velligan, D. I., Sajatovic, M., Hatch, A., Kramata, P., & Docherty, J. P. (2017). Why do psychiatric patients stop antipsychotic medication? A systematic review of reasons for nonadherence to medication in patients with serious mental illness. *Patient Prefer Adherence*, 11, 449-468. https://doi.org/ 10.2147/PPA.S124658

Xu, F., Fan, W., Wang, W., Tang, W., Yang, F., Zhang, Y., Cai, J., Song, L., & Zhang, C. (2019). Effects of Omega-3 Fatty acids on metabolic syndrome in patients with schizophrenia: A 12-week randomized placebo-controlled trial. *Psychopharmacology*, *236*(41273-1279. 10.1007/s00213-018-5136-9

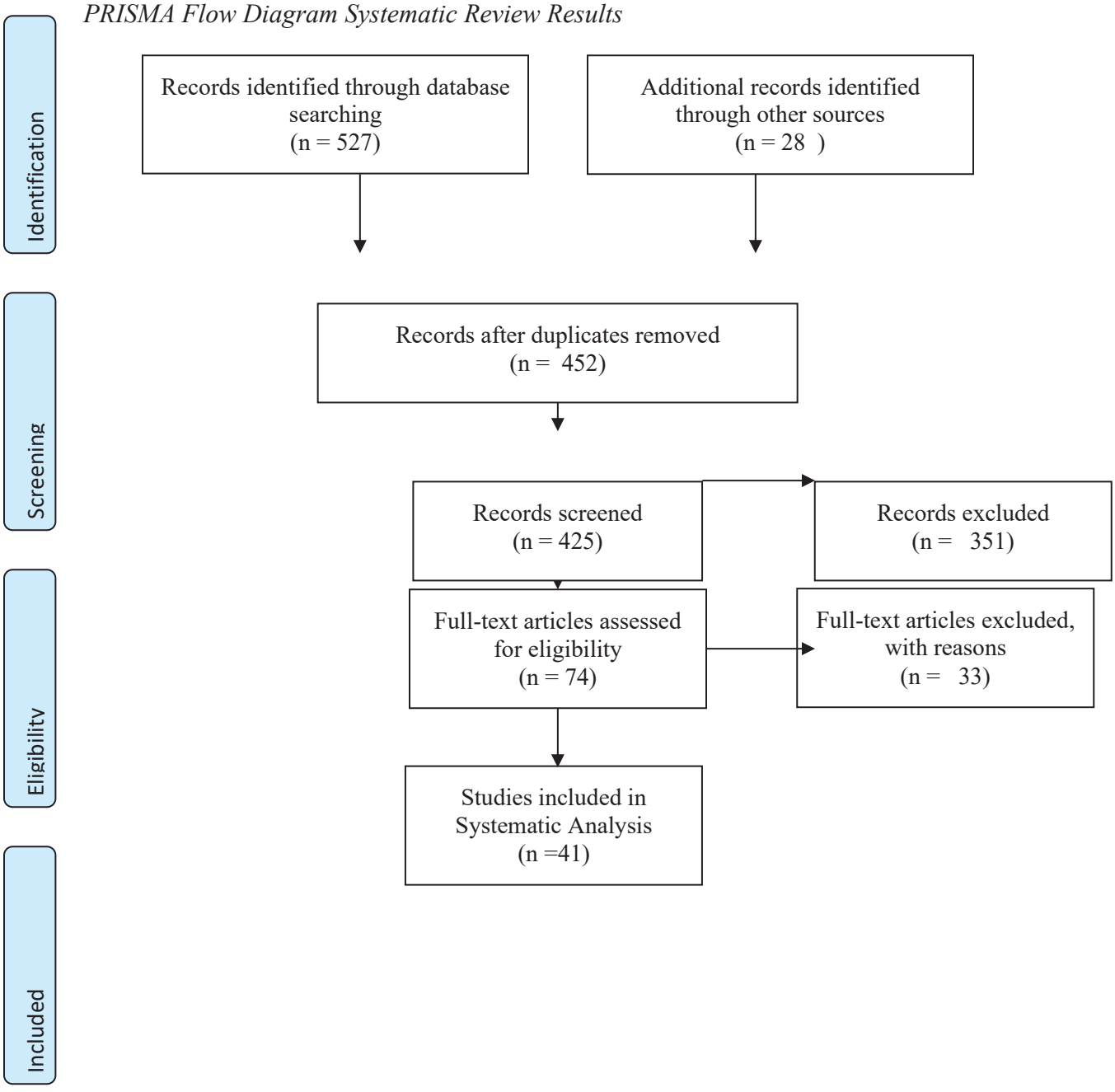
Yohn, S. E., Alberati, D., Correa, M., & Salamone, J. D. (2017). Assessment of a glycine uptake inhibitor in animal models of effort-related choice behavior: Implications for motivational dysfunctions. *Psychopharmacology*, *234*(9-10), 1525-1534. https://doi.org/10.1007/s00213-016-4523-3

Young, L. M., Pipingas, A., White, D. J., Gauci, S., & Scholey, A. (2019). A systematic review and meta-analysis of B Vitamin supplementation on depressive symptoms, anxiety, and stress: effects on healthy and 'at-risk' individuals. *Nutrients*, *11*(9), 2232. https://doi.org/10.3390/nu11092232

Appendix A: PRISMA Search Strategy and Results

Figure 1

PRISMA Flow Diagram Systematic Review Results



Appendix B: Literature Search Results

Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.

For the systematic review, the following databases were reviewed: PubMed, EBSCO Host and Database, CINHAL, EMBASE, ICTRP, CT.GOV, and COCHRANE Database. The information described in these results is also depicted in the PRISMA flow diagram. The included inclusion criteria was peer-reviewed journal articles in the last ten years (e.g., 2010 to 2020) regarding the effect of nutrition on mental health of individuals in the United States. In alignment with the research question, the following key words were used to search the noted databases: *nutrition and mental health, supplementation and mental health, diet and mental health, whole food and mental health, treating depression with nutrition, treating anxiety with nutrition, treating schizophrenia or psychotic disorders with nutrition, treatment of mental health disorders with nutritional methods, diet and mental health, diet and treating mental health.*

The total records identified through database search was 547 eligible articles. A sum of 28 articles were also included from the previously developed literature review. Of the 547 plus 28 articles, 452 were duplicates. Thus, a total of 452 articles were screened. After screening the initial 452 articles, a total of 351 articles were excluded. The removed articles were excluded if they did not follow the priori exclusion and inclusion criteria.

A total of 74 articles were identified for eligibility as full-text articles. These final 74 articles were reviewed, which resulted in exclusion of 33 articles that were excluded after examination and comparison with the inclusion and exclusion criteria. For example, in some of the excluded articles the nutritional and supplementation analysis was based on post-partum psychosis or mental health disorders that resulted from cystic ovary development in female populations. In cases such as these, the articles were removed as they did not meet the inclusion and exclusion criteria. Further, the nutritional and supplementation analysis was focused towards treating or addressing medical issues associated with gynecological concerns, which was not directly related to mental health. A final sum of 41 articles were delineated and logged to be included in the final discussion of results for the systematic review.

For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.

1. **Citation:**
    a. Amini, M., Bahmani, F., Foroozanfard, F., Vahedpoor, Z., Ghaderi, A., Taghizadeh, M., ... & Asemi, Z. (2020). The effects of fish oil omega-3 fatty acid supplementation on mental health parameters and metabolic status of patients with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial. *Journal of Psychosomatic Obstetrics & Gynecology*, 1-9. https://doi.org/10.1080/0167482X.2018.150828
    b. **Study Size:**
        i. 60 women with PCOS, aged 18–40 years old
    c. **Design**

i. Participants were randomly assigned into two groups to receive either 2 × 1000 mg/day fish oil omega-3 fatty acid ($n = 30$) or placebo ($n = 30$) after lunch for 12 weeks. Metabolic profiles were quantified at baseline and after the 12-week intervention.

d. Results

i. Compared with the placebo, omega-3 fatty acid intake led to a significant improvement in Beck Depression Inventory general health questionnaire and depression anxiety and stress scale Omega-3 fatty acid supplementation significantly decreased serum insulin homeostasis model of assessment-insulin resistance total testosterone and hirsutism and significantly increased the quantitative insulin sensitivity check index (compared with the placebo. Additionally, omega-3 fatty acid intake resulted in a significant decrease in high sensitivity C-reactive) and malondialdehyde also significant rises in plasma total glutathione was observed compared with the placebo. Omega-3 fatty acid supplementation did not change other metabolic parameters.

e. Notes or Recommendations, and Limitations

i. Overall, omega-3 fatty acid supplementation for 12 weeks to patients with PCOS had beneficial effects on mental health parameters, insulin metabolism, total testosterone, hirsutism and few inflammatory markers and oxidative stress.

2. Citation:

a. Ari, C., Kovács, Z., Juhasz, G., Murdun, C., Goldhagen, C. R., Koutnik, A. P., ... & D'Agostino, D. P. (2017). Exogenous ketone supplements reduce anxiety-related behavior in Sprague-Dawley and Wistar Albino Glaxo/Rijswijk rats. *Frontiers in molecular neuroscience*, *9*, 137. https://doi.org/10.3389/fnmol.2016.00137

b. Study Size:

i. We tested exogenous ketone supplements added to food and fed chronically for 83 days in SPD rats and administered sub-chronically for 7 days in both rat models by daily intragastric gavage bolus followed by assessment of anxiety measures on elevated plus maze (EPM).

c. Design

i. At the end of treatments behavioral data collection was conducted manually by a blinded observer and with a video-tracking system, after which blood βHB and glucose levels were measured. Ketone supplementation reduced anxiety on EPM as measured by less entries to closed arms (sub-chronic KE and KS: SPD rats and KSMCT: WAG/Rij rats), more time spent in open arms (sub-chronic KE: SPD and KSMCT: WAG/Rij rats; chronic KSMCT: SPD rats), more distance traveled in open arms (chronic KS and KSMCT: SPD rats) and by delayed latency to entrance to closed arms (chronic KSMCT: SPD rats), when compared to control.

d. Results

i. Our data indicates that chronic and sub-chronic ketone supplementation not only elevated blood βHB levels in both animal models, but reduced anxiety-related behavior. We conclude that ketone supplementation may represent a promising anxiolytic strategy through a novel means of inducing nutritional ketosis.

e. Notes or Recommendations, and Limitations

i. Non-human trial

3. Citation:

a. Bjelland, I., Tell, G. S., Vollset, S. E., Konstantinova, S., & Ueland, P. M. (2009). Choline in anxiety and depression: the Hordaland Health Study. *The American journal of clinical nutrition*, *90*(4), 1056-1060.

b. Study Size:

i. a subsample (n = 5918) of the Hordaland Health Study, including both sexes and 2 age groups of 46–49 and 70–74 y

c. Design

i. We studied a subsample (n = 5918) of the Hordaland Health Study, including both sexes and 2 age groups of 46–49 and 70–74 y who had valid information on plasma choline concentrations and symptoms of anxiety and depression measured by the Hospital Anxiety and Depression Scale—the latter 2 as continuous measures and dichotomized at a score ≥8 for both subscales

d. Results

i. The lowest choline quintile was significantly associated with high anxiety levels (odds ratio: 1.33; 95% CI: 1.06, 1.69) in the fully adjusted (age group, sex, time since last meal, educational level, and smoking habits) logistic regression model. Also, the trend test in the anxiety model was significant (P = 0.007). In the equivalent fully adjusted linear regression model, a significant inverse association was found between choline quintiles and anxiety levels (standardized regression coefficient = −0.027, P = 0.045). We found no significant associations in the corresponding analyses of the relation between plasma choline and depression symptoms.

e. Notes or Recommendations, and Limitations

i. In this large population–based study, choline concentrations were negatively associated with anxiety symptoms but not with depression symptoms.

4. Citation:

a. Ganança, L., Galfalvy, H. C., Oquendo, M. A., Hezghia, A., Cooper, T. B., Mann, J. J., & Sublette, M. E. (2017). Lipid correlates of antidepressant response to omega-3 polyunsaturated fatty acid supplementation: A pilot study. *Prostaglandins, Leukotrienes and Essential Fatty Acids*, *119*, 38-44. https://doi.org/10.1016/j.plefa.2017.03.004

b. Study Size:

i. 16 patients with symptomatic major depressive disorder, and tested plasma phospholipid levels of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) as correlates of clinical response.

c. Design

i. the higher the proportion of DHA to EPA, the greater the reduction in depression severity (r=−0.43, p=0.097). Five patients showed a decrease of ≥50% on the 17-item Hamilton Depression Rating Scale and a final score <7 and were thus not only responders but met standard criteria for remission, and were distinguished from non-responders by higher levels of DHA% (p=0.03).

d. Results

i. the higher the proportion of DHA to EPA, the greater the reduction in depression severity (r=−0.43, p=0.097). Five patients showed a decrease of ≥50% on the 17-item Hamilton Depression Rating Scale and a final score <7 and were thus not only responders but met standard criteria for remission, and were distinguished from non-responders by higher levels of DHA% (p=0.03).

e. Notes or Recommendations, and Limitations

i. n/a

5. Citation:

i. Greenwood, L. M., Leung, S., Michie, P. T., Green, A., Nathan, P. J., Fitzgerald, P., ... & Croft, R. J. (2018). The effects of glycine on auditory mismatch negativity in schizophrenia. *Schizophrenia research*, *191*, 61-69. https://doi.org/10.1016/j.schres.2017.05.031

b. Study Size:

i. This study aimed to determine the effects of acute and 6-week chronic glycine administration on MMN in schizophrenia patients. MMN amplitude was compared at baseline between 22 patients (schizophrenia or schizoaffective disorder; receiving stable antipsychotic medication; multi-centre recruitment) and 21 age- and gender-matched controls

c. Design

i. Patients underwent a randomised, double-blind, placebo-controlled clinical trial with glycine added to their regular antipsychotic medication (placebo, n = 10; glycine, n = 12). MMN was reassessed post-45-minutes of first dose (0.2 g/kg) and post-6-weeks treatment (incremented to 0.6 g/kg/day). Clinical symptoms were assessed at baseline and post-6-weeks treatment

d. Results

i. At baseline, duration MMN was smaller in schizophrenia compared to controls. Acute glycine increased duration MMN (compared to placebo), whilst this difference was absent post-6-weeks treatment. Six weeks of chronic glycine administration improved PANSS-Total, PANSS-Negative and PANSS-General symptoms compared to placebo. Smaller baseline duration MMN was associated with greater PANSS-Negative symptoms and predicted (at trend level) PANSS-Negative symptom improvement post-6-weeks glycine treatment (not placebo). These findings support the

benefits of chronic glycine administration and demonstrate, for the first time, that acute glycine improves duration MMN in schizophrenia. This result, together with smaller baseline duration MMN predicting greater clinical treatment response, suggests the potential for duration MMN as a biomarker of glycine-induced improvements in negative symptoms in schizophrenia.

e. Notes or Recommendations, and Limitations

i. n/a

6. Citation:

i. Grønli, O., Kvamme, J. M., Friborg, O., & Wynn, R. (2013). Zinc deficiency is common in several psychiatric disorders. *PloS one*, *8*(12), e82793. https://doi.org/10.1371/journal.pone.0082793

b. Study Size:

i. Clinical data and blood samples for zinc analyzes were collected from 100 psychogeriatric patients over 64 of age. Control group of 882 individuals.

c. Design

i. Psychiatric and cognitive symptoms were assessed using the Montgomery and Aasberg Depression Rating Scale, the Cornell Scale for Depression in Dementia, the Mini-Mental State Examination, the Clockdrawing Test, clinical interviews and a review of medical records. In addition, a diagnostic interview was conducted using the Mini International Neuropsychiatric Interview instrument. The prevalence of zinc deficiency in patients with depression was compared with the prevalence in patients without depression, and the prevalence in a control group of 882 older persons sampled from a population study.

d. Results

i. There was a significant difference in zinc deficiency prevalence between the control group (14.4%) and the patient group (41.0%) (χ^2=44.81, df=1, p<0.001). In a logistic model with relevant predictors, zinc deficiency was positively associated with gender and with serum albumin level. The prevalence of zinc deficiency in the patient group was significantly higher in patients without depression (i.e. with other diagnoses) than in patients with depression as a main diagnosis or comorbid depression (χ^2=4.36, df=1, p=0.037).

7. Citation:

i. Imtiaz, S., Ikram, H., Ayaz, M., Qadir, M. I., & Muhammad, S. A. (2018). Effect of glycine: Studying memory and behavioral changes in mice. *Pakistan journal of pharmaceutical sciences*, *31*(5).

b. Study Size:

i. We investigated the effect of different doses of glycine on memory and behavior using 30 albino mice models (treated and control)

c. Design

i. After two weeks of glycine dosing, we performed light and dark activity and novel-object recognition (NOR) tests to assess the cognitive traits.

Brain and blood samples were taken and kept at -70°C using ultra-low temperature freezer. Neurochemical estimation of blood glycine level was estimated by high-performance liquid chromatography with electrochemical detectors (HPLC-ECD)

d. Results

i. Concentration of glycine (100, 300 and 500 mg/kg) is significantly observed ($p<0.01$) and it changes due to physiological variations in N-methyl-D- aspartate (NMDA) an important neurotransmitter for memory. We observed significant increase in serotonin metabolites including 5-hydroxy tryptophan (5-HT, $p<0.05$) and 5-hydroxy indole acetic acid (5-HIAA, $p<0.001$) levels. Similarly, effects were found in case of dopamine (DA, $p<0.05$) and its metabolites: 3, 4-Dihydroxyphenylacetic acid (DOPAC, $p<0.001$) and homovanillic acid (HVA, $p<0.001$). Histopathological investigation of brain tissues showed cellular clumps at cortical junctions at higher doses of glycine as compared to control. These findings revealed that dose dependent concentration of glycine can be useful for memory loss and behavior deficits.

8. Citation:

i. Jacka, F. N., Mykletun, A., Berk, M., Bjelland, I., & Tell, G. S. (2011). The association between habitual diet quality and the common mental disorders in community-dwelling adults: the Hordaland Health study. *Psychosomatic medicine*, *73*(6), 483-490.

b. Study Size:

i. This cross-sectional study included 5731 population-based men and women aged 46 to 49 and 70 to 74 years

c. Design

i. Habitual diet was assessed using a validated food frequency questionnaire, and mental health was measured using the Hospital Anxiety and Depression Scale

d. Results

i. Concentration of glycine (100, 300 and 500 mg/kg) is significantly observed ($p<0.01$) and it changes due to physiological variations in N-methyl-D- aspartate (NMDA) an important neurotransmitter for memory. We observed significant increase in serotonin metabolites including 5-hydroxy tryptophan (5-HT, $p<0.05$) and 5-hydroxy indole acetic acid (5-HIAA, $p<0.001$) levels. Similarly, effects were found in case of dopamine (DA, $p<0.05$) and its metabolites: 3, 4-Dihydroxyphenylacetic acid (DOPAC, $p<0.001$) and homovanillic acid (HVA, $p<0.001$). Histopathological investigation of brain tissues showed cellular clumps at cortical junctions at higher doses of glycine as compared to control. These findings revealed that dose dependent concentration of glycine can be useful for memory loss and behavior deficits.

ii. After adjustments for variables including age, education, income, physical activity, smoking, and alcohol consumption, an *a priori*healthy diet quality score was inversely related to depression (odds ratio [OR] = 0.71, 95% confidence interval [CI] = 0.59-0.84) and anxiety(OR = 0.77, 95% CI =

0.68-0.87) in women and to depression (OR = 0.83, 95% CI = 0.70-0.99) in men. Women scoring higher on a healthy dietary pattern were less likely to be depressed (OR = 0.68, 95% CI = 0.57-0.82) or anxious (OR = 0.87, 95% CI = 0.77-0.98), whereas men were more likely to be anxious (OR = 1.19, 95% CI = 1.03-1.38). A traditional Norwegian dietary pattern was also associated with reduced depression in women (OR = 0.77, 95% CI = 0.64-0.92) and anxiety in men (OR = 0.77, 95% CI = 0.61-0.96). A western-type diet was associated with increased anxiety in men (OR = 1.27, 95% CI = 1.14-1.42) and women (OR = 1.29, 95% CI = 1.17-1.43) before final adjustment for energy intake.

9. Citation:

a. Messaoudi, M., Violle, N., Bisson, J. F., Desor, D., Javelot, H., & Rougeot, C. (2011). Beneficial psychological effects of a probiotic formulation (Lactobacillus helveticus R0052 and Bifidobacterium longum R0175) in healthy human volunteers. *Gut microbes*, *2*(4), 256-261. https://doi.org/10.4161/gmic.2.4.16108

b. Study Size:

i. 25

c. Design

i. his addendum presents a secondary analyze of the effects of PF in a sub-population of 25 subjects with urinary free cortisol (UFC) levels less than 50 ng/ml at baseline, on psychological distress based on the percentage of change of the perceived stress scale (PSs), the HADs and the HSCL-90 scores between baseline and follow-up

d. Results

i. The data show that PF improves the same scores as in the general population (the HADs global score, the global severity index of the HSCL-90 and three of its sub-scores, i.e. somatization, depression and anger-hostility), as well as the PSs score and three other sub-scores of the HSCL-90, i.e. "obsessive compulsive", "anxiety", and "paranoid-ideation". Moreover, in the HSCL-90, the score of the Factor 1, related to anxiety and depression, is significantly improved over time in PF-treated subjects compared with controls.

10. Citation:

i. Mohammadi, A. A., Jazayeri, S., Khosravi-Darani, K., Solati, Z., Mohammadpour, N., Asemi, Z., ... & Eghtesadi, S. (2016). The effects of probiotics on mental health and hypothalamic–pituitary–adrenal axis: A randomized, double-blind, placebo-controlled trial in petrochemical workers. *Nutritional neuroscience*, *19*(9), 387-395. https://doi.org/10.1179/1476830515Y.0000000023

b. Study Size:

i. 70 petrochemical workers

c. Design

i. The present randomized double-blind, placebo-controlled trial was conducted on 70 petrochemical workers. Subjects were randomly divided into three groups to receive 100 g/day probiotic yogurt + one placebo

capsule ($n = 25$) or one probiotic capsule daily + 100 g/day conventional yogurt ($n = 25$) or 100 g/day conventional yogurt + one placebo capsule ($n = 20$) for 6 weeks. Mental health parameters including general health questionnaire (GHQ) and depression anxiety and stress scale (DASS) scores were measured. Fasting blood samples were obtained at the beginning and 6 weeks after the intervention to quantify hypothalamic–pituitary–adrenal axis.

d. Results

i. After 6 weeks of intervention, a significant improvement of GHQ was observed in the probiotic yogurt (18.0 ± 1.5 vs. 13.5 ± 1.9, $P = 0.007$) and in the probiotic capsule group (16.9 ± 1.8 vs. 9.8 ± 1.9, $P = 0.001$), as well as a significant improvement in DASS scores in the probiotic yogurt (23.3 ± 3.7 vs. 13.0 ± 3.7, $P = 0.02$) and the probiotic capsule group (18.9 ± 3.2 vs. 9.4 ± 4.0, $P = 0.006$). However, there was no significant improvement in the conventional yogurt group ($P = 0.05$ for GHQ and $P = 0.08$ for DASS) The consumption of probiotic yogurt or a multispecies probiotic capsule had beneficial effects on mental health parameters in petrochemical workers.

11. Citation:

i. Neufeld, K. M., Kang, N., Bienenstock, J., & Foster, J. A. (2011). Reduced anxiety-like behavior and central neurochemical change in germ-free mice. *Neurogastroenterology & Motility*, *23*(3), 255-e119. https://doi.org/10.1111/j.1365-2982.2010.01620.x

b. Study Size:

i. Did not report.

c. Design

i. We investigated basal behavior of adult germ-free (GF), Swiss Webster female mice in the elevated plus maze (EPM) and compared this to conventionally reared specific pathogen free (SPF) mice. Additionally, we measured brain mRNA expression of genes implicated in anxiety and stress-reactivity.

d. Results

i. Germ-free mice, compared to SPF mice, exhibited basal behavior in the EPM that can be interpreted as anxiolytic. Altered GF behavior was accompanied by a decrease in the N-methyl-D-aspartate receptor subunit NR2B mRNA expression in the central amygdala, increased brain-derived neurotrophic factor expression and decreased serotonin receptor 1A (5HT1A) expression in the dentate granule layer of the hippocampus. We conclude that the presence or absence of conventional intestinal microbiota influences the development of behavior, and is accompanied by neurochemical changes in the brain.

12. Citation:

i. Papalini, S., Michels, F., Kohn, N., Wegman, J., Van Hemert, S., Roelofs, K., ... & Aarts, E. (2019). Stress matters: randomized controlled trial on

the effect of probiotics on neurocognition. *Neurobiology of stress*, *10*, 100141. https://doi.org/10.1016/j.ynstr.2018.100141

b. Study Size:

i. In a double blind, randomized, placebo-controlled, between-subjects intervention study, 58 healthy participants were tested once before and once after a 28-day intervention

c. Design

i. We investigated the effects of a multispecies probiotic (Ecologic®Barrier) on specific neurocognitive measures of emotion reactivity, emotion regulation, and cognitive control using fMRI. Critically, we also tested whether probiotics can buffer against the detrimental effects of acute stress on working memory. In a double blind, randomized, placebo-controlled, between-subjects intervention study, 58 healthy participants were tested once before and once after a 28-day intervention.

d. Results

i. Without stress induction, probiotics did not affect brain, behavioral, or related self-report measures. However, relative to placebo, the probiotics group did show a significant stress-related increase in working memory performance after supplementation. This change was associated with intervention-related neural changes in frontal cortex during cognitive control exclusively in the probiotics group. Overall, our results show neurocognitive effects of a multispecies probiotic in healthy women only under challenging situations, buffering against the detrimental effects of stress on cognition.

13. Citation:

i. Sudo, N., Chida, Y., Aiba, Y., Sonoda, J., Oyama, N., Yu, X. N., ... & Koga, Y. (2004). Postnatal microbial colonization programs the hypothalamic–pituitary–adrenal system for stress response in mice. *The Journal of physiology*, *558*(1), 263-275. https://doi.org/10.1113/jphysiol.2004.063388

b. Study Size:

i. Not stated

c. Design

i. To test the idea that such microbes may affect the development of neural systems that govern the endocrine response to stress, we investigated hypothalamic–pituitary–adrenal (HPA) reaction to stress by comparing germfree (GF), specific pathogen free (SPF) and gnotobiotic mice.

d. Results

i. Pasma ACTH and corticosterone elevation in response to restraint stress was substantially higher in GF mice than in SPF mice, but not in response to stimulation with ether. Moreover, GF mice also exhibited reduced brain-derived neurotrophic factor expression levels in the cortex and hippocampus relative to SPF mice. The exaggerated HPA stress response by GF mice was reversed by reconstitution with *Bifidobacterium infantis*.

In contrast, monoassociation with enteropathogenic *Escherichia coli*, but not with its mutant strain devoid of the translocated intimin receptor gene, enhanced the response to stress. Importantly, the enhanced HPA response of GF mice was partly corrected by reconstitution with SPF faeces at an early stage, but not by any reconstitution exerted at a later stage, which therefore indicates that exposure to microbes at an early developmental stage is required for the HPA system to become fully susceptible to inhibitory neural regulation. These results suggest that commensal microbiota can affect the postnatal development of the HPA stress response in mice.

14. Citation:

i. Xu, F., Fan, W., Wang, W., Tang, W., Yang, F., Zhang, Y., ... & Zhang, C. (2019). Effects of omega-3 fatty acids on metabolic syndrome in patients with schizophrenia: a 12-week randomized placebo-controlled trial. *Psychopharmacology*, *236*(4), 1273-1279. 10.1007/s00213-018-5136-9

b. Study Size:

i. recruited 80 patients with both schizophrenia and MetS who received long-term olanzapine monotherapy. The patients were randomly assigned to the OMG-3 group ($n = 40$) or the placebo group ($n = 40$).

c. Design

i. This study employed a randomized placebo-controlled trial to investigate the effects of omega-3 fatty acids on MetS in patients with schizophrenia.

d. Results

i. Patients with both schizophrenia and MetS had significantly higher levels of TNF-alpha than the control subjects ($Z = -4.37$, $P < 0.01$). There was a significant correlation between omega-3 fatty acid treatment and reduced triglyceride (TG) levels ($F_{\text{group} \times \text{time}} = 13.42$; df = 1, 66; $P < 0.01$) when the patients completed this study. Along with metabolic improvement, omega-3 fatty acids decreased TNF-alpha levels after 12 weeks of treatment ($F_{\text{group} \times \text{time}} = 6.71$; df = 1, 66; $P = 0.012$). We also found that the extent of TNF-alpha decrease was significantly correlated with that of TG decrease ($r = 0.38$, $P = 0.001$).

15. Citation:

i. Yohn, S. E., Alberati, D., Correa, M., & Salamone, J. D. (2017). Assessment of a glycine uptake inhibitor in animal models of effort-related choice behavior: implications for motivational dysfunctions. *Psychopharmacology*, *234*(9-10), 1525-1534. DOI 10.1007/s00213-016-4523-3

b. Study Size:

i. Did not state

c. Design

i. Effort-based choice in rats was assessed using the concurrent fixed ratio (FR) 5/chow feeding choice task and the T-maze barrier choice procedure.

d. Results

i. Haloperidol shifted effort-based choice, biasing ani- mals towards the low effort option in each task. Co- administration of bitopertin (1.0–10.0 mg/kg) significantly attenuated haloperidol-induced shifts in choice behavior, but the same doses of bitopertin had no effect when administered alon hese results indicated that elevation of extracel- lular glycine via inhibition of glycine uptake was able to re- verse the effects of D2 antagonism. Increases in extracellular glycine, possibly through actions on the glycine allosteric site on the NMDA receptor, may be a useful strategy for treating motivational dysfunctions in humans.

16. Citation:

i. Kiecolt-Glaser, J. K., Belury, M. A., Andridge, R., Malarkey, W. B., & Glaser, R. (2011). Omega-3 supplementation lowers inflammation and anxiety in medical students: a randomized controlled trial. *Brain, behavior, and immunity*, *25*(8), 1725-1734. https://doi.org/10.1016/j.bbi.2011.07.229

b. Study Size:

i. The participants, 68 medical students, provided serial blood samples during lower-stress periods as well as on days before an exam

c. Design

i. The students received either *n*-3 (2.5 g/d, 2085 mg eicosapentaenoic acid and 348 mg docosahexanoic acid) or placebo capsules that mirrored the proportions of fatty acids in the typical American diet.

d. Results

i. Compared to controls, those students who received *n*-3 showed a 14% decrease in lipopolysaccharide (LPS) stimulated interleukin 6 (IL-6) production and a 20% reduction in anxiety symptoms, without significant change in depressive symptoms. Individuals differ in absorption and metabolism of *n*-3 PUFA supplements, as well as in adherence; accordingly, planned secondary analyses that used the plasma *n*-6:*n*-3 ratio in place of treatment group showed that decreasing *n*-6:*n*-3 ratios led to lower anxiety and reductions in stimulated IL-6 and tumor necrosis factor alpha (TNF-α) production, as well as marginal differences in serum TNF-α. These data suggest that *n*-3 supplementation can reduce inflammation and anxiety even among healthy young adults.

17. Citation:

i. Slykerman, R. F., Hood, F., Wickens, K., Thompson, J. M. D., Barthow, C., Murphy, R., ... & Probiotic in Pregnancy Study Group. (2017). Effect of Lactobacillus rhamnosus HN001 in pregnancy on postpartum symptoms of depression and anxiety: a randomised double-blind placebo-controlled trial. *EBioMedicine*, *24*, 159-165. https://doi.org/10.1016/j.ebiom.2017.09.013

b. Study Size:

i. 380 women

c. Design

i. We conducted a double-blind placebo-controlled study of probiotic (*Lactobacillus rhamnosus* HN001) supplementation (from early pregnancy through to 6 months after delivery if breastfeeding) on postnatal symptoms of depression and anxiety in a group (n = 380) of healthy women

d. Results

i. Mothers in the probiotic treatment group reported significantly lower depression and anxiety scores than those in the placebo group.

18. Citation:

i. Kehr, J., Yoshitake, T., Ichinose, F., Yoshitake, S., Kiss, B., Gyertyán, I., & Adham, N. (2018). Effects of cariprazine on extracellular levels of glutamate, GABA, dopamine, noradrenaline and serotonin in the medial prefrontal cortex in the rat phencyclidine model of schizophrenia studied by microdialysis and simultaneous recordings of locomotor activity. *Psychopharmacology*, *235*(5), 1593-1607. https://link.springer.com/article/10.1007/s00213-018-4874-z

b. Study Size:

i. 7 rats

c. Design

i. Microdialysis was performed in awake rats with probes placed into the mPFC. Rats (n = 7/group) received vehicle (saline), cariprazine (0.05, 0.2, or 0.8 mg/kg), or aripiprazole (3 or 20 mg/kg) via gavage. After 60 min, 5 mg/kg PCP was administered intraperitoneally (i.p.). Samples were taken before drug administration, during pretreatment, and after PCP injection. Locomotor activity recording and microdialysis sampling occurred simultaneously.

d. Results

i. Microdialysis was performed in awake rats with probes placed into the mPFC. Rats (n = 7/group) received vehicle (saline), cariprazine (0.05, 0.2, or 0.8 mg/kg), or aripiprazole (3 or 20 mg/kg) via gavage. After 60 min, 5 mg/kg PCP was administered intraperitoneally (i.p.). Samples were taken before drug administration, during pretreatment, and after PCP injection. Locomotor activity recording and microdialysis sampling occurred simultaneously.

19. Citation:

i. De Koning, E. J., Van der Zwaluw, N. L., Van Wijngaarden, J. P., Sohl, E., Brouwer-Brolsma, E. M., Van Marwijk, H. W., ... & De Groot, L. C. (2016). Effects of two-year vitamin B12 and folic acid supplementation on depressive symptoms and quality of life in older adults with elevated homocysteine concentrations: additional results from the B-PROOF study, an RCT. *Nutrients*, *8*(11), 748.

b. Study Size:
   i. 2919 p

c. Design
   i. Lowering elevated plasma homocysteine (Hcy) concentrations by supplementing vitamin B_{12} and folic acid may reduce depressive symptoms and improve health-related quality of life (HR-QoL) in older adults. This study aimed to test this hypothesis in a randomized controlled trial. Participants (N = 2919, ≥65 years, Hcy concentrations ≥12 µmol/L) received either 500 µg vitamin B_{12} and 400 µg folic acid daily or placebo for two years. Both tablets contained 15 µg vitamin D_3. Depressive symptoms were measured with the Geriatric Depression Scale-15 (GDS-15). HR-QoL was assessed with the SF-12 Mental and Physical component summary scores and the EQ-5D Index score and Visual Analogue Scale.

d. Results
   i. Differences in two-year change scores were analyzed with Analysis of Covariance (ANCOVA). Hcy concentrations decreased more in the intervention group, but two-year change scores of the GDS-15 and three of four HR-QoL measures did not differ between groups. The EQ-5D Index score declined less in the intervention group than in the placebo group (mean change 0.00 vs. −0.02, p = 0.004). In conclusion, two-year supplementation with vitamin B_{12} and folic acid in older adults with hyperhomocysteinemia showed that lowering Hcy concentrations does not reduce depressive symptoms, but it may have a small positive effect on HR-QoL

20. Citation:

   i. Föcker, M., Antel, J., Grasemann, C., Führer, D., Timmesfeld, N., Öztürk, D., ... & Libuda, L. (2018). Effect of an vitamin D deficiency on depressive symptoms in child and adolescent psychiatric patients–a randomized controlled trial: study protocol. *BMC psychiatry*, *18*(1), 57. https://link.springer.com/article/10.1186/s12888-018-1637-7

b. Study Size:
   i. 200

c. Design
   i. This double blinded, randomized controlled trial will enroll 200 inpatients from school-aged children psychiatric department with a vitamin D deficiency defined by a 25(OH)-vitamin D-level < 30 nmol/l (12 ng/ml) and a Beck Depressions Inventory (BDI-II) score > 13 (indicating at least: mild depression). Upon referral, all patients will be screened, checked for inclusion criteria, and those eligible will be randomized after written consent into a supplementation or placebo group. Both study-arms will receive treatment-as-usual for their psychiatric disorder according to established clinical guidelines. The participants of the vitamin D supplementation group will receive 2640 I.E. vitamin D3 q.d. for 28 days

in accordance with best practice in pediatric endocrinology. We hypothesize that delaying supplementation of vitamin D in the placebo arm will affect the treatment success of the depressive symptomatology in comparison to the vitamin D supplementation group. Patients will be enrolled for a period of 28 days based on the mean length of hospitalization of juveniles with depression.

d. Results

i. Randomized controlled trials in children and adolescents with depression are needed to elucidate the role of a vitamin D deficiency for mental disorders and to investigate the relevance of a routine assessment and supplementation of vitamin D deficits.

21. Citation:

i. Rondanelli, M., Giacosa, A., Opizzi, A., Pelucchi, C., La Vecchia, C., Montorfano, G., ... & Rizzo, A. M. (2011). Long chain omega 3 polyunsaturated fatty acids supplementation in the treatment of elderly depression: effects on depressive symptoms, on phospholipids fatty acids profile and on health-related quality of life. *The journal of nutrition, health & aging*, *15*(1), 37-44.

b. Study Size:

i. *Subjects:* Forty-six depressed females, aged 66-95 years. *Intervention:* 22 depressed females were included in the intervention group (n-3 group, that received 2.5 g/day of n-3 LCPUFA, with 1.67 grams of EPA and 0.83 grams of DHA), and 24 patients in the placebo group.

c. Design

i. Recent observations showed that long chain omega 3 polyunsaturated fatty acids (n-3 LCPUFA) could represent a potential treatment for elderly depression. To determine if a n-3 LCPUFA containing supplement improves depressive symptoms, changes phospholipids acids profile and ameliorates Health related quality of life (HRQoL) in depressed elderly patients. *Design:* Two-months, randomized, double-blind, placebo-controlled trial. *Setting:* Nursing home in Pavia, Italy. *Subjects:* Forty-six depressed females, aged 66-95 years. *Intervention:* 22 depressed females were included in the intervention group (n-3 group, that received 2.5 g/day of n-3 LCPUFA, with 1.67 grams of EPA and 0.83 grams of DHA), and 24 patients in the placebo group.

d. Results

i. The primary endpoint was the improvement of depressive symptoms as evaluated by Geriatric Depression Scale (GDS). Secondary endpoints were the evaluation of modifications of erythrocyte membrane phospholipids fatty acid profile and of of HRQoL, by using the Short-Form 36- Item Health Survey (SF-36). All parameters were assessed before and after the treatment period of 8 weeks. *Results:* The mean GDS at 2 months was significantly lowered only for the n-3 group. SF-36 physical and mental components were significantly increased in the

intervention group. Compliance was good, as confirmed by erythrocyte membrane phospholipid FA concentrations, with significant increase of EPA and DHA in the intervention group. *Conclusion:* The supplementation of n-3 LCPUFA in elderly female patients reduces the occurrence of depressive symptoms, improves phospholipids fatty acids profile and health- related quality of life.

22. Citation:

i. van de Rest, O., Geleijnse, J. M., Kok, F. J., van Staveren, W. A., Hoefnagels, W. H., Beekman, A. T., & de Groot, L. C. (2008). Effect of fish-oil supplementation on mental well-being in older subjects: a randomized, double-blind, placebo-controlled trial. *The American journal of clinical nutrition*, *88*(3), 706-713. https://doi.org/10.1093/ajcn/88.3.706

b. Study Size:

i. *302*

c. Design

i. Independently living individuals (*n* = 302) aged ≥65 y were randomly assigned to consume 1800 mg/d EPA+DHA, 400 mg/d EPA+DHA, or placebo capsules for 26 wk. Changes in mental well-being were assessed as the primary outcome with the Center for Epidemiologic Studies Depression Scale (CES-D), Montgomery-Åsberg Rating Scale (MADRS), Geriatric Depression Scale (GDS-15), and Hospital Anxiety and Depression Scale (HADS-A).

d. Results

i. Plasma concentrations of EPA+DHA increased by 238% in the high-dose and 51% in the low-dose fish-oil group compared with the placebo group, reflecting excellent compliance. Baseline CES-D scores ranged from 5.9 to 6.8 in the 3 groups and were not significantly different between groups. Mean changes in CES-D scores after 26 wk were −0.2, 0.2, and −0.4 (*P* = 0.87) in the high-dose fish oil, low-dose fish oil, and placebo groups, respectively. Treatment with neither 1800 mg nor 400 mg EPA+DHA differentially affected any of the measures of mental well-being after 13 or

ii. 26 week of intervention compared with placebo.

23. Citation:

i. Smesny, S., Milleit, B., Hipler, U. C., Milleit, C., Schäfer, M. R., Klier, C. M., ... & Amminger, G. P. (2014). Omega-3 fatty acid supplementation changes intracellular phospholipase A 2 activity and membrane fatty acid profiles in individuals at ultra-high risk for psychosis. *Molecular psychiatry*, *19*(3), 317-324. https://www.nature.com/articles/mp20137

b. Study Size:

i. *81*

c. Design

i. n a randomized placebo-controlled trial, we have identified long-chain ω-3 (ω-3) polyunsaturated fatty acid (PUFA) supplementation as potentially

useful, as it reduced the rate of transition to psychosis by 22.6% 1 year after baseline in a cohort of 81 young people at UHR of transition to psychosis. However, the mechanisms whereby the ω-3 PUFAs might be neuroprotective are incompletely understood. Here, we report on the effects of ω-3 PUFA supplementation on intracellular phospholipase A_2 (*in*PLA_2) activity, the main enzymes regulating phospholipid metabolism, as well as on peripheral membrane lipid profiles in the individuals who participated in this randomized placebo-controlled trial. Patients were studied cross-sectionally (n=80) and longitudinally (n=65) before and after a 12-week intervention with 1.2 g per day ω-3 PUFAs or placebo, followed by a 40-week observation period to establish the rates of transition to psychosis. We investigated *in*PLA_2 and erythrocyte membrane FAs in the treatment groups (ω-3 PUFAs vs placebo) and the outcome groups (psychotic vs non-psychotic)

d. Results

i. The levels of membrane ω-3 and ω-6 PUFAs and *in*PLA_2 were significantly related. Some of the significant associations (that is, long-chain ω-6 PUFAs, arachidonic acid) with *in*PLA_2 activity were in opposite directions in individuals who did (a positive correlation) and who did not (a negative correlation) transition to psychosis. Supplementation with ω-3 PUFA resulted in a significant decrease in *in*PLA_2 activity. We conclude that ω-3 PUFA supplementation may act by normalizing *in*PLA_2 activity and δ-6-desaturase-mediated metabolism of ω-3 and ω-6 PUFAs, suggesting their role in neuroprogression of psychosis.

24. Citation:

i. Gariballa, S., Forster, S., Walters, S., & Powers, H. (2006). A randomized, double-blind, placebo-controlled trial of nutritional supplementation during acute illness. *The American journal of medicine*, *119*(8), 693-699. https://doi.org/10.1016/j.amjmed.2005.12.006

b. Study Size:

i. 45 hospitalized patients aged 65 to 92 years

ii.

c. Design

i. In this randomized, double-blind, placebo-controlled study, we randomly assigned 445 hospitalized patients aged 65 to 92 years to receive either a normal hospital diet plus 400 mL oral nutritional supplements (223 subjects) or a normal hospital diet plus a placebo (222 subjects) daily for 6 weeks. The composition of the supplement was such as to provide 995 kcal of energy and 100% of the Reference Nutrient Intakes for vitamins and minerals for a healthy older person. Patients had three assessments: at baseline, at 6 weeks, and at 6 months post-randomization. Outcome measures were 6 months of disability, non-elective readmission and length of hospital stay, discharge destination, morbidity, and mortality.

d. Results

i. Randomization to the supplement group led to a significant improvement in nutritional status. Over 6 months, 65 patients (29%) in the supplements group were readmitted to the hospital compared with 89 patients (40%) in the placebo group (adjusted hazard ratio 0.68 [95% confidence interval 0.49-0.94]). The mean length of hospital stay was 9.4 days in the supplements group compared with 10.1 days in the placebo group. Thirty-two people (14%) died in the supplement group compared with 19 people (9%) in the placebo group at 6 months (adjusted hazard ratio 1.65 [95% confidence interval, 0.93-2.92]).

25. Citation:

i. Pawełczyk, T., Grancow, M., Kotlicka-Antczak, M., Trafalska, E., Gębski, P., Szemraj, J., ... & Pawełczyk, A. (2015). Omega-3 fatty acids in first-episode schizophrenia-a randomized controlled study of efficacy and relapse prevention (OFFER): rationale, design, and methods. *BMC psychiatry*, *15*(1), 97. https://link.springer.com/article/10.1186/s12888-015-0473-2

b. Study Size:

i. 82 patients

c. Design

i. A randomized placebo-controlled one-center trial will be used to compare the efficacy of 26-week intervention, composed of either 1320 mg/day of EPA and 880 mg/day of DHA, or olive oil placebo with regard to symptom severity and relapse rate in first-episode schizophrenia patients. Eighty-two patients (aged 16–35) will be recruited for the study. Eligible patients will be randomly allocated to one of two intervention arms: an active arm or a placebo arm (olive oil). The primary outcome measure of the clinical evaluation is schizophrenia symptom severity measured by the Positive and Negative Syndrome Scale (PANSS). Other outcomes include depressive symptoms, patient functioning and the level of insight. Correlates of change measured during the study will include structural brain changes, oxidative stress and defense, as well as neuroplasticity indicators. Metabolic syndrome components will also be assessed throughout the study.

d. Results

i. By comparing 26-week administration of EPA + DHA or (placebo) olive oil as add-on therapy in reducing symptom severity and one-year relapse rate in patients with first episode schizophrenia, it is intended to provide new insights into the efficacy of omega-3 PUFA and correlates of change, and contribute to the improvement of mental health care for individuals suffering from schizophrenia.

26. Citation:

i. Grung, B., Sandvik, A. M., Hjelle, K., Dahl, L., Frøyland, L., Nygård, I., & Hansen, A. L. (2017). Linking vitamin D status, executive functioning

and self-perceived mental health in adolescents through multivariate analysis: A randomized double-blind placebo control trial. *Scandinavian journal of psychology*, *58*(2), 123-130. https://doi.org/10.1111/sjop.12353

b. Study Size:

i. 50

c. Design

i. The aim of the present randomized double-blind placebo control trial was to investigate if vitamin D supplementation had an effect on vitamin D status, executive functioning and self-perceived mental health in a group of Norwegian adolescents during winter time. Fifty late adolescents were randomly assigned into an intervention group (vitamin D pearls) or a control group (placebo pearls). Before (pre-test in December/January) and after (post-test in April/May) the intervention period the participants were exposed to a test procedure, consisting of blood draw, completion of cognitive tests (Tower of Hanoi and Tower of London), and the Youth Self-report version of the Child Behavior Checklist.

d. Results

i. Multivariate data analysis showed that participants with low vitamin D status scored worse on the Tower of London (ToL) tests and the more difficult sub-tasks on the Tower of Hanoi tests. They also had a tendency to report higher frequency of externalizing behavior problems and attention deficit. At pre-test, the overall mean vitamin D status measured as 25-hydroxy vitamin D was 42 nmol/L, defining deficiency (Intervention group = 44 nmol/L, Control group = 39 nmol/L). However, vitamin D supplementation caused a significant increase in vitamin D status resulting in a sufficient level in the Intervention group at post-test (mean 62 nmol/L). The results also revealed that the intervention group improved their performance on the most demanding sub-tasks on the ToH. Overall, the study indicates that vitamin D status in adolescents may be important for both executive functioning and mental health.

27. Citation:

i. Adan, R. A., van der Beek, E. M., Buitelaar, J. K., Cryan, J. F., Hebebrand, J., Higgs, S., ... & Dickson, S. L. (2019). Nutritional psychiatry: towards improving mental health by what you eat. *European Neuropsychopharmacology*, *29*(12), 1321-1332. https://doi.org/10.1016/j.euroneuro.2019.10.011

b. Study Size:

i. 50

c. Design

i. Systematic review

d. Results

i. Future studies should focus on elucidating mechanism. Randomized controlled trials should be of high quality, adequately powered and geared towards the advancement of knowledge from population-based

observations towards personalized nutrition. Here, we provide an overview of the emerging field of nutritional psychiatry, exploring the scientific evidence exemplifying the importance of a well-balanced diet for mental health. We conclude that an experimental medicine approach and a mechanistic understanding is required to provide solid evidence on which future policies on diet and nutrition for mental health can be based.

e. Limitation

i. Bias possible due to lack of clear methodology used for systematic review.

28. Citation:

i. Teasdale, S. B., Ward, P. B., Samaras, K., Firth, J., Stubbs, B., Tripodi, E., & Burrows, T. L. (2019). Dietary intake of people with severe mental illness: systematic review and meta-analysis. *The British Journal of Psychiatry*, *214*(5), 251-259.

b. Study Size:

i. Six electronic databases were searched for studies reporting on dietary intakes in psychotic disorders and bipolar disorder. Dietary-assessment methods, and dietary intakes, were systematically reviewed. Where possible, data was pooled for meta-analysis and compared with healthy controls.

c. Design

i. Systematic review

d. Results

i. In total, 58 eligible studies were identified. People with severe mental illnesses were found to have significantly higher dietary energy (mean difference 1332 kJ, 95% CI 487–2178 kJ/day, $P = 0.002$, $g = 0.463$) and sodium (mean difference 322 mg, 95% CI 174–490 mg, $P < 0.001$, $g = 0.414$) intake compared with controls. Qualitative synthesis suggested that higher energy and sodium intakes were associated with poorer diet quality and eating patterns.

e. Limitation

i. Clear strategy used for the systematic review, however, not a controlled study or empirical data used .

29. Citation:

i. Allen, A. P., Dinan, T. G., Clarke, G., & Cryan, J. F. (2017). A psychology of the human brain–gut–microbiome axis. *Social and personality psychology compass*, *11*(4), e12309. https://doi.org/10.1111/spc3.12309

b. Study Size:

i. n/a

c. Design

i. Systematic review

d. Results

i. In recent years, we have seen increasing research within neuroscience and biopsychology on the interactions between the brain, the gastrointestinal tract, the bacteria within the gastrointestinal tract, and the bidirectional relationship between these systems: the brain–gut–microbiome axis. Although research has demonstrated that the gut microbiota can impact upon cognition and a variety of stress-related behaviours, including those relevant to anxiety and depression, we still do not know how this occurs. A deeper understanding of how psychological development as well as social and cultural factors impact upon the brain–gut–microbiome axis will contextualize the role of the axis in humans and inform psychological interventions that improve health within the brain–gut–microbiome axis. Interventions ostensibly aimed at ameliorating disorders in one part of the brain–gut–microbiome axis (e.g., psychotherapy for depression) may nonetheless impact upon other parts of the axis (e.g., microbiome composition and function), and functional gastrointestinal disorders such as irritable bowel syndrome represent a disorder of the axis, rather than an isolated problem either of psychology or of gastrointestinal function. The discipline of psychology needs to be cognizant of these interactions and can help to inform the future research agenda in this emerging field of research. In this review, we outline the role psychology has to play in understanding the brain–gut–microbiome axis, with a focus on human psychology and the use of research in laboratory animals to model human psychology.

e. Limitation

i. Bias possible due to lack of clear methodology used for systematic review.

30. Citation:

i. Herrera, A., Munoz, P., Steinbusch, H. W., & Segura-Aguilar, J. (2017). Are dopamine oxidation metabolites involved in the loss of dopaminergic neurons in the nigrostriatal system in Parkinson's disease?. *ACS Chemical Neuroscience*, *8*(4), 702-711.

b. Study Size:

i. n/a

c. Design

i. Systematic review

d. Results

i. Currently, it is widely accepted that the degeneration of dopaminergic neurons, i.e., in the substantia nigra pars compacta, involves mitochondrial dysfunction, the formation of neurotoxic oligomers of alpha-synuclein, the dysfunction of protein degradation systems, neuroinflammation, and oxidative and endoplasmic reticulum stress. However, the initial trigger of these mechanisms in the nigrostriatal system is still unknown. It has been reported that aminochrome induces the majority of these mechanisms involved in the neurodegeneration process. Aminochrome is formed

within the cytoplasm of neuromelanin-containing dopaminergic neurons during the oxidation of dopamine to neuromelanin. The oxidation of dopamine to neuromelanin is a normal and harmless process, because healthy individuals have intact neuromelanin-containing dopaminergic neurons. Interestingly, aminochrome-induced neurotoxicity is prevented by two enzymes: DT-diaphorase and glutathione transferase M2-2, which explains why melanin-containing dopaminergic neurons are intact in healthy human brains

e. Limitation

i. Bias possible due to lack of clear methodology used for systematic review.

31. Citation:

i. Holloway, J. B. (2016). The Role of Herbal and Nutraceutical Supplementation in the Amelioration of Schizophrenia and Schizoaffective Symptomology. *Scientia et Humanitas*, *6*, 95-114.

b. Study Size:

i. n/a

c. Design

i. Systematic review

d. Results

i. Herbal supplements are used increasingly in both developed and undeveloped countries for purposes of prevention, delaying onset, decreasing overall severity, and potential reversal of mental illness. The purpose of this overview is to present the latest empirical findings regarding the efficacy of various herbal and nutraceutical supplements in the prevention, treatment, and delaying onset of symptomology in relation to schizophrenia and other schizoaffective disorders, as well as further to explore their potential role in the future of psychiatry and related health practices. The supplements and their efficacy examined in this literature overview are Omega-3 fatty acids, Curcumin, Folic Acid, B12, B6, vitamin D, N-acetylcysteine, SAM-e, Bocopa Monniera, Ginkgo Biloba, Iron, Glycine, (?)–Stepholidine, Yokukansan, Orengadoku, and Ficus Platyphylla.

e. Limitation

i. Bias possible due to lack of clear methodology used for systematic review.

32. Citation:

i. Berridge, M. J. (2017). Vitamin D and depression: cellular and regulatory mechanisms. *Pharmacological reviews*, *69*(2), 80-92.

b. Study Size:

i. n/a

c. Design

i. Systematic review

d. Results

i. Depression is caused by a change in neural activity resulting from an increase in glutamate that drives excitatory neurons and may be responsible for the decline in the activity and number of the GABAergic inhibitory neurons. This imbalance between the excitatory and inhibitory neurons may contribute to the onset of depression. At the cellular level there is an increase in the concentration of intracellular Ca^{2+} within the inhibitory neurons that is driven by an increase in entry through the NMDA receptors (NMDARs) and through activation of the phosphoinositide signaling pathway that generates inositol trisphosphate ($InsP_3$) that releases Ca^{2+} from the internal stores. The importance of these two pathways in driving the elevation of Ca^{2+} is supported by the fact that depression can be alleviated by ketamine that inhibits the NMDARs and scopolamine that inhibits the M1 receptors that drive $InsP_3/Ca^{2+}$ pathway. This increase in Ca^{2+} not only contributes to depression but it may also explain why individuals with depression have a strong likelihood of developing Alzheimer's disease. The enhanced levels of Ca^{2+} may stimulate the formation of Aβ to initiate the onset and progression of Alzheimer's disease. Just how vitamin D acts to reduce depression is unclear. The phenotypic stability hypothesis argues that vitamin D acts by reducing the increased neuronal levels of Ca^{2+} that are driving depression. This action of vitamin D depends on its function to maintain the expression of the Ca^{2+} pumps and buffers that reduce Ca^{2+} levels, which may explain how it acts to reduce the onset of depression.

e. Limitation

i. Bias possible due to lack of clear methodology used for systematic review.

33. Citation:

i. Jamilian, H., Amirani, E., Milajerdi, A., Kolahdooz, F., Mirzaei, H., Zaroudi, M., ... & Asemi, Z. (2019). The effects of vitamin D supplementation on mental health, and biomarkers of inflammation and oxidative stress in patients with psychiatric disorders: A systematic review and meta-analysis of randomized controlled trials. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *94*, 109651. https://doi.org/10.1016/j.pnpbp.2019.109651

b. Study Size:

i. n/a

c. Design

i. The following databases were search up to March 2019: MEDLINE, EMBASE, Web of Science, and Cochrane Central Register of Controlled Trials. The quality of the relevant extracted data was assessed according to the Cochrane risk of bias tool. Data were pooled by the use of the inverse variance method and expressed as mean difference with 95% Confidence Intervals (95% CI).

d. Results

i. Eleven effect sizes from nine studies were included in the final analyses. A pooled analysis of 9 effect sizes showed a significant reduction in Beck Depression Inventory (BDI) score following supplementation with vitamin D [weighted mean difference (WMD): -3.91; 95% CI: -5.15 -2.66), I^2= 85.9%]. Combining data from two available studies on the effects of vitamin D supplementation on Pittsburgh Sleep Quality Index (PSQI) also revealed a significant reduction in this score following the intervention (WMD: -1.78; 95% CI: -2.28, -1.28). In addition, there were significant increase in glutathione (GSH) through 3 studies (WMD: 180.70; 95% CI: 6.76, 354.64), and in total antioxidant capacity (TAC) through 3 studies (WMD: 90.09; 95% CI: 56.36, 123.82) after vitamin D supplementation. Combining data from five studies, we found a significant reduction in C-reactive protein (CRP) concentrations after vitamin D supplementation (WMD: -1.74; 95% CI: -2.82, -0.66).

e. Limitation

i. Clear strategy used for the systematic review, however, not a controlled study or empirical data used .

34. Citation:

i. Khanna, P., Chattu, V. K., & Aeri, B. T. (2019). Nutritional aspects of depression in adolescents-A systematic review. *International journal of preventive medicine*, *10*. https://dx.doi.org/10.4103%2Fijpvm.IJPVM_400_18

b. Study Size:

i. n/a

c. Design

i. As part of the systematic review, around 1000 relevant articles published between January 1978 and December 2017 were identified by systematic online search from 6 electronic databases (PubMed, PsycInfo, Science Direct, MEDLINE, Scopus, and Google Scholar) and overall, 56 relevant studies were included in the current review as per the inclusion criteria. Findings highlight the potential importance of the relationship between healthy dietary patterns or quality and positive mental health throughout life span.

d. Results

i. Various nutrition and dietary compounds have been suggested to be involved in the onset maintenance and severity of depressive symptoms and disorders. Nutritional compounds might modulate depression associated biomarkers. In this context, several healthy foods such as olive oil, fish, nuts, legumes, dairy products, fruits, and vegetables have been inversely associated with the risk of depression and might also improve symptoms. In contrast western dietary patterns including the consumption of sweetened beverages, fried foods, processed meats, baked products have been shown to be associated with an increased risk of depression in longitudinal studies. Diet and nutrition offer key modifiable targets for the prevention of mental disorders. Evidence is steadily growing for the

relation between nutrition deficiencies, diet quality and mental health and for the efficacy and use of nutritional supplements to address deficiencies or as augmentation therapies. We advocate recognition of diet and nutrition as crucial factors in prevention and management of mental disorders.

e. Limitation

i. Clear strategy used for the systematic review, however, not a controlled study or empirical data used .

35. Citation:

i. Jamilian, H., Amirani, E., Milajerdi, A., Kolahdooz, F., Mirzaei, H., Zaroudi, M., ... & Asemi, Z. (2019). The effects of vitamin D supplementation on mental health, and biomarkers of inflammation and oxidative stress in patients with psychiatric disorders: A systematic review and meta-analysis of randomized controlled trials. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *94*, 109651. https://doi.org/10.1016/j.pnpbp.2019.109651

b. Study Size:

i. n/a

c. Design

i. The following databases were search up to March 2019: MEDLINE, EMBASE, Web of Science, and Cochrane Central Register of Controlled Trials. The quality of the relevant extracted data was assessed according to the Cochrane risk of bias tool. Data were pooled by the use of the inverse variance method and expressed as mean difference with 95% Confidence Intervals (95% CI).

d. Results

i. Eleven effect sizes from nine studies were included in the final analyses. A pooled analysis of 9 effect sizes showed a significant reduction in Beck Depression Inventory (BDI) score following supplementation with vitamin D [weighted mean difference (WMD): -3.91; 95% CI: -5.15 -2.66), I^2= 85.9%]. Combining data from two available studies on the effects of vitamin D supplementation on Pittsburgh Sleep Quality Index (PSQI) also revealed a significant reduction in this score following the intervention (WMD: -1.78; 95% CI: -2.28, -1.28). In addition, there were significant increase in glutathione (GSH) through 3 studies (WMD: 180.70; 95% CI: 6.76, 354.64), and in total antioxidant capacity (TAC) through 3 studies (WMD: 90.09; 95% CI: 56.36, 123.82) after vitamin D supplementation. Combining data from five studies, we found a significant reduction in C-reactive protein (CRP) concentrations after vitamin D supplementation (WMD: -1.74; 95% CI: -2.82, -0.66).

e. Limitation

i. Clear strategy used for the systematic review, however, not a controlled study or empirical data used .

36. Citation:

i. McEwen, B., & Fenasse, R. (2019). Probiotics and depression:'The link between the microbiome-gut-brain axis and digestive and mental health'. *Journal of the Australian Traditional-Medicine Society*, *25*(3), 127.

b. Study Size:

i. n/a

c. Design

i. Systematic Review

d. Results

i. It has been hypothesised for years that a gut-brain connection exists. The gutbrain connection can often be described as having a 'gut feeling' or commonly that 'sinking feeling' - that sensation of nausea when anxious. Recently, there has been an increased interest in the influence of intestinal microbiota on mental health. It is thought that the intestinal microbiota influences the brain mainly through the vagus nerve by humoral and neural means of the gutbrain axis.

e. Limitation

i. Bias due to lack of clear strategy for review of literature.

37. Citation:

i. Olagunju, A., Gatchel, J. R., Morgan, J. A., Aftab, A., Chen, P. P., Dols, A., ... & Regenold, W. T. (2019). Nutrition and Bipolar Disorders in Older Adults: A systematic Review. *The American Journal of Geriatric Psychiatry*, *27*(3), S207-S208. https://doi.org/10.1016/j.jagp.2019.01.119

b. Study Size:

i. n/a

c. Design

i. We searched databases including Medline/PubMed, PsychINFO, EMBASE, CINAHL, Scopus, Web of Science, Cochrane Register FDA, and clinical trial registries till May 2018 for eligible reports. The search string combined MeSH terms for Bipolar disorder, nutrition and older adults. This was supplemented by snowball searching of references of included studies and relevant reviews for additional studies. Data extraction was done by at least two persons independently.

d. Results

i. Fifteen studies that included a subpopulation of OABD were included. The topic foci of the papers include nutrition's (including vitamins B_{12}, vitamin D, folate, homocysteine, and creatinine) deficiencies, use of herbal-nutritional products, influence of nutrients on affective and cognitive outcomes, and relationship of nutritional factors with MRI measures of white matter densities. The sample sizes of OABD are generally small and follow-up is limited.

e. Limitation

i. Clear strategy used for the systematic review, however, not a controlled study or empirical data used .

38. Citation:

i. Young, L. M., Pipingas, A., White, D. J., Gauci, S., & Scholey, A. (2019). A Systematic Review and Meta-Analysis of B Vitamin Supplementation on Depressive Symptoms, Anxiety, and Stress: Effects on Healthy and 'At-Risk'Individuals. *Nutrients*, *11*(9), 2232. https://doi.org/10.3390/nu11092232

b. Study Size:

i. n/a

c. Design

i. A systematic review and meta-analysis was undertaken to examine and quantify the effects of B vitamin supplementation on mood in both healthy and 'at-risk' populations. A systematic search identified all available randomised controlled trials (RCTs) of daily supplementation with ≥3 B group vitamins with an intervention period of at least four weeks. Random effects models for a standardized mean difference were used to test for overall effect. Heterogeneity was tested using the I^2 statistic. Eighteen articles (16 trials, 2015 participants) were included, of which 12 were eligible for meta-analysis.

d. Results

i. Eleven of the 18 articles reported a positive effect for B vitamins over a placebo for overall mood or a facet of mood. Of the eight studies in 'at-risk' cohorts, five found a significant benefit to mood. Regarding individual facets of mood, B vitamin supplementation benefited stress (n = 958, SMD = 0.23, 95% CI = 0.02, 0.45, p = 0.03). A benefit to depressive symptoms did not reach significance (n = 568, SMD = 0.15, 95% CI = −0.01, 0.32, p = 0.07), and there was no effect on anxiety (n = 562, SMD = 0.03, 95% CI = −0.13, 0.20, p = 0.71). The review provides evidence for the benefit of B vitamin supplementation in healthy and at-risk populations for stress, but not for depressive symptoms or anxiety. B vitamin supplementation may particularly benefit populations who are at risk due to (1) poor nutrient status or (2) poor mood statu

e. Limitation

i. Clear strategy used for the systematic review, however, not a controlled study or empirical data used .

39. Citation:

i. Firth, J., Carney, R., Stubbs, B., Teasdale, S. B., Vancampfort, D., Ward, P. B., ... & Sarris, J. (2018). Nutritional deficiencies and clinical correlates in first-episode psychosis: a systematic review and meta-analysis. *Schizophrenia bulletin*, *44*(6), 1275-1292.

b. Study Size:

i. n/a

c. Design

i. A search of electronic databases conducted in July 2017 identified 28 eligible studies, examining blood levels of 6 vitamins and 10 minerals across 2612 individuals: 1221 individuals with FEP and 1391 control subjects. Meta-analyses compared nutrient levels in FEP to nonpsychiatric controls. Clinical correlates of nutritional status in patient samples were systematically reviewed.

d. Results

i. Significantly lower blood levels of folate ($N = 6$, $n = 827$, $g = -0.624$, 95% confidence interval [CI] = −1.176 to −0.072, $P = .027$) and vitamin D ($N = 7$, $n = 906$, $g = -1.055$, 95% CI = −1.99 to −0.119, $P = .027$) were found in FEP compared to healthy controls. Synthesis of clinical correlates found both folate and vitamin D held significant inverse relationships with psychiatric symptoms in FEP. There was also limited evidence for serum level reductions of vitamin C ($N = 2$, $n = 96$, $g = -2.207$, 95% CI = −3.71 to −0.71, $P = .004$). No differences were found for other vitamins or minerals.

e. Limitation

i. Clear strategy used for the systematic review, however, not a controlled study or empirical data used .

40. Citation:

i. Bae, J. H., & Kim, G. (2018). Systematic review and meta-analysis of omega-3-fatty acids in elderly patients with depression. *Nutrition Research*, *50*, 1-9. https://doi.org/10.1016/j.nutres.2017.10.013

b. Study Size:

i. Systematic Review

c. Design

i. This analysis was conducted to provide evidence for the clinical application of omega-3 fatty acids in the treatment of depressive symptoms of elderly subjects older than 65 years. Seven databases were searched from their inception date until September 2016. Following this search, 6 studies were selected, which included 4605 patients (mean age, 76.97 years; male-female ratio = 3752:853; mean dose of omega 3 intake, 1.3 g/d).

d. Results

i. These results were divided into 2 categories: well-being mental health group and depressive group. In the well-being mental health group, the Hedges *g* was 0.12 (95% confidence interval, −0.05 to 0.29), which indicated no significant effect of n-3 PUFA supplementation on depressed mood compared with placebo. In the depressive group, the pooled Hedges *g* was −0.94 (95% CI, −1.37 to −0.50]) for the random-effects model, which indicated a large effect of n-3 PUFA supplementation on those with depressed mood compared with placebo. Although this review

shows that omega-3 fatty acids are effective in the treatment of elderly depressed patients, the benefits of omega-3 fatty acid supplementation were significant only in the elderly patients with mild to moderate depression.

e. Limitation

i. Clear strategy used for the systematic review, however, not a controlled study or empirical data used .

41. Citation:

i. Mikkelsen, K., Stojanovska, L., Prakash, M., & Apostolopoulos, V. (2017). The effects of vitamin B on the immune/cytokine network and their involvement in depression. *Maturitas*, *96*, 58-71. https://doi.org/10.1016/j.maturitas.2016.11.012

b. Study Size:

i. n/a

c. Design

i. n/a

d. Results

i. Increasing evidence indicates that there are various interactions between the nervous system and the immune system, and that the immune system plays an important role in the pathogenesis of depression. Pro-inflammatory cytokines (such as IL-1, IL-6, TNF-α) have been implicated in the neurobiological manifestations of depression. The immune/cytokine network has a powerful influence on the brain. In addition, deficiency in B vitamins has been linked to depression. Hence, greater knowledge of how immune cells change in the presence of vitamin B derivatives could improve understanding of how immune changes may correlate with depression, all of which are discussed herein.

e. Limitation

i. Bias due to lack of clear strategy for review of literature.

Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).

Outcome level assessment was not performed for this systematic review. However, the most notable biases in the reviewed articles was present in the systematic reviews relevant to the inclusion criteria. In these systematic review, there was a some evidence of approaches that did not clearly define the methodology used for systematic review. in terms of the empirical literature, the use of mice samples does limit the understanding of the application

of findings for human trials, which necessities further research. In the presentation of results and discussion, each study will be discussed alongside limitations present for systematic reviews and empirical literature.

For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.

For this systematic review, 16 of the studies used systematic review approaches. In terms of empirical literature, the designs used included randomized double-blind placebo controlled studies, controlled examinations in human and mice trials, cross-sectional analyses, blood sample and clinical data assessments using baseline and intervention assessments, basal behavior comparisons in mice samples, multivariate analysis of secondary data, and intervention studies. Detailed discussion of these findings and an overview of the reviewed literature will be presented in Chapter Four and Five.

Appendix C: Database Results

Figure 2

Database Results

Database Results	Name	Results	Search Years
	EMBASE Seearch	98	2000-2020

Database Results	Name	Results	Search Years
	CT. Seearch	44	2000-2020

Database Results	Name	Results	Search Years
	COCHRANE Seearch	239	2000-2020

Database Results	Name	Results	Search Years
	COCHRANE Seearch	239	2000-2020

Databases Searched
PubMed, EBSCO Host and Database, CINHAl, EMBASE, ICTRP, CT.GOV, COCHRANE

Database Results	Name	Results	Search Years
	PubMed	103	200-2020

Database Results	Name	Results	Search Years
	EBSCO Host Seearch	No results were found	2000-2020

Database Results	Name	Results	Search Years
	CINHAL Seearch	3	2000-2020

Appendix D: Empirical Evidence for Treating Depression

Table 2

Empirical Evidence for Treating Major Depression Disorder

Topic	***Citations***
Depression	Bjelland, I., Tell, G. S., Vollset, S. E., Konstantinova, S., & Ueland, P. M. (2009). Choline in anxiety and depression: the Hordaland Health Study. *The American journal of clinical nutrition*, *90*(4), 1056-1060.
Depression	Ganança, L., Galfalvy, H. C., Oquendo, M. A., Hezghia, A., Cooper, T. B., Mann, J. J., & Sublette, M. E. (2017). Lipid correlates of antidepressant response to Omega-3 polyunsaturated fatty acid supplementation: A pilot study. *Prostaglandins, Leukotrienes and Essential Fatty acids* , *119*, 38-44. https://doi.org/10.1016/j.plefa.2017.03.004
Depression	Slykerman, R. F., Hood, F., Wickens, K., Thompson, J. M. D., Barthow, C., Murphy, R., ... & Probiotic in Pregnancy Study Group. (2017). Effect of Lactobacillus rhamnosus HN001 in pregnancy on postpartum symptoms of depression and anxiety: a randomized, double-blind placebo-controlled trial. *EBioMedicine*, *24*, 159-165. https://doi.org/10.1016/j.ebiom.2017.09.013
Depression	De Koning, E. J., Van der Zwaluw, N. L., Van Wijngaarden, J. P., Sohl, E., Brouwer-Brolsma, E. M., Van Marwijk, H. W., ... & De Groot, L. C. (2016). Effects of two-year Vitamin B12 and folic acid supplementation on depressive symptoms and quality of life in older adults with elevated homocysteine concentrations: additional results from the B-PROOF study, an RCT. *Nutrients*, *8*(11), 748.
Depression	Föcker, M., Antel, J., Grasemann, C., Führer, D., Timmesfeld, N., Öztürk, D., ... & Libuda, L. (2018). Effect of a Vitamin D deficiency on depressive symptoms in child and adolescent psychiatric patients–a randomized controlled trial: study protocol. *BMC psychiatry*, *18*(1), 57. https://link.springer.com/article/10.1186/s12888-018-1637-7
Depression	Rondanelli, M., Giacosa, A., Opizzi, A., Pelucchi, C., La Vecchia, C., Montorfano, G., ... & Rizzo, A. M. (2011). Long chain Omega 3 polyunsaturated Fatty acids supplementation in treating elderly depression: effects on depressive symptoms, on phospholipids Fatty acids profile and health-related quality of life. *The journal of nutrition, health & aging*, *15*(1), 37-44.

Appendix E: Empirical Evidence for Treating Schizophrenia

Table 3

Empirical Evidence for Treating Schizophrenia

Topic	***Citations***
Schizophrenia	Pawełczyk, T., Grancow, M., Kotlicka-Antczak, M., Trafalska, E., Gębski, P., Szemraj, J., ... & Pawełczyk, A. (2015). Omega-3 Fatty acids in first-episode schizophrenia-a randomized controlled study of efficacy and relapse prevention (OFFER): rationale, design, and methods. *BMC psychiatry*, *15*(1), 97. https://doi.org/10.1186/s12888-015-0473-2
Schizophrenia	Greenwood, L. M., Leung, S., Michie, P. T., Green, A., Nathan, P. J., Fitzgerald, P., ... & Croft, R. J. (2018). The effects of glycine on auditory mismatch negativity in schizophrenia. *Schizophrenia Research*, *191*, 61-69. https://doi.org/10.1016/j.schres.2017.05.031
Schizophrenia	Xu, F., Fan, W., Wang, W., Tang, W., Yang, F., Zhang, Y., ... & Zhang, C. (2019). Effects of Omega-3 Fatty acids on metabolic syndrome in patients with schizophrenia: a 12-week randomized placebo-controlled trial. *Psychopharmacology*, *236*(4), 1273-1279. 10.1007/s00213-018-5136-9
Schizophrenia	Kehr, J., Yoshitake, T., Ichinose, F., Yoshitake, S., Kiss, B., Gyertyán, I., & Adham, N. (2018). Effects of cariprazine on extracellular levels of glutamate, GABA, dopamine, noradrenaline and serotonin in the medial prefrontal cortex in the rat phencyclidine model of schizophrenia studied by microdialysis and simultaneous recordings of locomotor activity. *Psychopharmacology*, *235*(5), 1593-1607. https://link.springer.com/article/10.1007/s00213-018-4874-z

Appendix F: Empirical Evidence for Treating Anxiety

Table 4

Empirical Evidence for Treating General Anxiety

Topic	***Citations***
Anxiety	Ari, C., Kovács, Z., Juhasz, G., Murdun, C., Goldhagen, C. R., Koutnik, A. P., ... & D'Agostino, D. P. (2017). Exogenous ketone supplements reduce anxiety-related behavior in Sprague-Dawley and Wistar Albino Glaxo/Rijswijk rats. *Frontiers in molecular neuroscience*, *9*, 137. https://doi.org/10.3389/fnmol.2016.00137
Anxiety	Kiecolt-Glaser, J. K., Belury, M. A., Andridge, R., Malarkey, W. B., & Glaser, R. (2011). Omega-3 supplementation lowers inflammation and anxiety in medical students: a randomized controlled trial. *Brain, behavior, and immunity*, *25*(8), 1725-1734. https://doi.org/10.1016/j.bbi.2011.07.229
Anxiety	Neufeld, K. M., Kang, N., Bienenstock, J., & Foster, J. A. (2011). Reduced anxiety-like behavior and central neurochemical change in germ-free mice. *Neurogastroenterology & Motility*, *23*(3), 255-e119. https://doi.org/10.1111/j.1365-2982.2010.01620.x

Appendix G: Empirical Evidence for Treating General Disorders

Table 5

Empirical Evidence for General Disorders (E.g., Multiple Disorders in the Same Examination)

Topic	***Citations***
Omega-3 Fatty acids Depression, Anxiety, and Chronic Illness	Amini, M., Bahmani, F., Foroozanfard, F., Vahedpoor, Z., Ghaderi, A., Taghizadeh, M., ... & Asemi, Z. (2020). The effects of fish oil Omega-3 fatty acid supplementation on patients' mental health parameters and metabolic status with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial. *Journal of Psychosomatic Obstetrics & Gynecology*, 1-9. https://doi.org/10.1080/0167482X.2018.150828
Zinc and Various Psychiatric Disorders	Grønli, O., Kvamme, J. M., Friborg, O., & Wynn, R. (2013). Zinc deficiency is common in several psychiatric disorders. *PloS one*, *8*(12), e82793. https://doi.org/10.1371/journal.pone.0082793
Glycine and Behavioral Changes (Mice)	Imtiaz, S., Ikram, H., Ayaz, M., Qadir, M. I., & Muhammad, S. A. (2018). Effect of glycine: Studying memory and behavioral changes in mice. *Pakistan Journal of pharmaceutical sciences*, *31*(5).
Mental Disorders and Diet Quality	Jacka, F. N., Mykletun, A., Berk, M., Bjelland, I., & Tell, G. S. (2011). The association between habitual diet quality and the common mental disorders in community-dwelling adults: the Hordaland Health study. *Psychosomatic medicine*, *73*(6), 483-490.
Probiotic and Psychological Effect	Messaoudi, M., Violle, N., Bisson, J. F., Desor, D., Javelot, H., & Rougeot, C. (2011). Beneficial psychological effects of a probiotic formulation (Lactobacillus helveticus R0052 and Bifidobacterium longum R0175) in healthy human volunteers. *Gut microbes*, *2*(4), 256-261. https://doi.org/10.4161/gmic.2.4.16108
Probiotics and Mental Health	Mohammadi, A. A., Jazayeri, S., Khosravi-Darani, K., Solati, Z., Mohammadpour, N., Asemi, Z., ... & Eghtesadi, S. (2016). The effects of probiotics on mental health and hypothalamic–pituitary–adrenal axis: A randomized, double-blind, placebo-controlled trial in petrochemical workers. *Nutritional neuroscience*, *19*(9), 387-395. https://doi.org/10.1179/1476830515Y.0000000023
Probiotics and Stress	Papalini, S., Michels, F., Kohn, N., Wegman, J., Van Hemert, S., Roelofs, K., ... & Aarts, E. (2019). Stress matters: randomized controlled trial on the effect of probiotics on neurocognition. *Neurobiology of stress*, *10*, 100141. https://doi.org/10.1016/j.ynstr.2018.100141

Microbiota and Stress	Sudo, N., Chida, Y., Aiba, Y., Sonoda, J., Oyama, N., Yu, X. N., ... & Koga, Y. (2004). Postnatal microbial colonization programs the hypothalamic–pituitary–adrenal system for stress response in mice. *The Journal of physiology*, *558*(1), 263-275. https://doi.org/10.1113/jphysiol.2004.063388
Glycine and Behavior	Yohn, S. E., Alberati, D., Correa, M., & Salamone, J. D. (2017). Assessment of a glycine uptake inhibitor in animal models of effort-related choice behavior: implications for motivational dysfunctions. *Psychopharmacology*, *234*(9-10), 1525-1534. DOI 10.1007/s00213-016-4523-3
Fish oil and Mental Well Being	van de Rest, O., Geleijnse, J. M., Kok, F. J., van Staveren, W. A., Hoefnagels, W. H., Beekman, A. T., & de Groot, L. C. (2008). Effect of fish-oil supplementation on mental well-being in older subjects: a randomized, double-blind, placebo-controlled trial. *The American journal of clinical nutrition*, *88*(3), 706-713. https://doi.org/10.1093/ajcn/88.3.706
Omega-3 Fatty acids and Psychosis Risk	Smesny, S., Milleit, B., Hipler, U. C., Milleit, C., Schäfer, M. R., Klier, C. M., ... & Amminger, G. P. (2014). Omega-3 fatty acid supplementation changes intracellular phospholipase A 2 activity and membrane fatty acid profiles in individuals at ultra-high risk for psychosis. *Molecular psychiatry*, *19*(3), 317-324. https://www.nature.com/articles/mp20137
Nutritional Supplementation in Acute Illness	Gariballa, S., Forster, S., Walters, S., & Powers, H. (2006). A randomized, double-blind, placebo-controlled trial of nutritional supplementation during acute illness. *The American journal of medicine*, *119*(8), 693-699. https://doi.org/10.1016/j.amjmed.2005.12.006
Vitamin D and Mental Health Perception	Grung, B., Sandvik, A. M., Hjelle, K., Dahl, L., Frøyland, L.,Nygård, I., & Hansen, A. L. (2017). Linking Vitamin D status, executive functioning, and self-perceived mental health in adolescents through multivariate analysis: A randomized double-blind placebo-control trial. *Scandinavian journal of psychology*, *58*(2), 123-130. https://doi.org/10.1111/sjop.12353

Appendix H: Quick Reference Charts

Table 6

Quick Fact Disorder, Neurotransmitter and Nutritional Supplement Reference

Mental Health Disorder	Neurotransmitter	Nutritional Supplement	The Findings	References
Generalized Anxiety Disorder	Dopamine and Serotonin, and acetylcholine	Exogenous ketone supplementation, B-vitamins, probiotics, magnesium, lysine, arginine, myo-inositol, and N-acetyl-cysteine, Vitamin D, Lactobacillus brevis, and choline	These supplements have been found to positively impact the neurotransmitters of Dopamine and Serotonin, and acetylcholine and can aid in reducing patients anxiety symptoms.	(Ari et al., 2017; Kiecolt-Glaser et al., 2011; Neufeld et al., 2011).
Major Depressive Disorder	Dopamine, glutamate and GABA neurotransmitters, Serotonin, monoamines, acetylcholine, and noradrenaline	Exogenous ketone supplementation, , B-vitamins, probiotics, magnesium, lysine, arginine, myo-inositol, and N-acetyl-cysteine, Vitamin D, Omega-3 fatty acids and amino acids	Each of these supplements are useful for targeting various neurotransmitters associated with depression. Taking these supplements daily can aid in reduction of depression symptoms.	(Bjelland et al., 2009; Gananca et al., 2017; Rondanelli et al., 2011; Slykerman et al., 2017).
Bipolar Disorder I and II	Dopamine, Serotonin, vanadium, and PUFA-biomarker	Cysteine, vitamin B, Vitamin B3, Nicotinic Acid (NA), and Omega-3	These supplements aid in the reduction of mania and other related bipolar disorder symptoms. Patients may benefit from	(Gronli et al., 2013; Imitiaz et al., 2018; Messaoudi et al., 2011).

			taking these daily.	
Schizophrenia	Dopamine	Cysteine, amino acids, glycine, and Omega-3	Each of these supplements are positively associated with reduction of schizophrenia symptoms through targeting the dopamine neurotransmitter.	(Greenwood et al., 2018; Kehr et al., 2018; Pawelczy et al., 2015; Xu et al., 2019).