Nutritional Neurosciences

Wael Mohamed
Firas Kobeissy *Editors*

Nutrition and Psychiatric Disorders

An Evidence-Based Approach to Understanding the Diet-Brain Connection

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Nutritional Neurosciences

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Editors

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I express heartfelt gratitude and deep appreciation as I dedicate this work to my wife, Dr. Rehab Ismaeil. Your unwavering support and unconditional love have been constant pillars throughout my academic journey and beyond. I am truly grateful for the love and inspiration you bring to my life, and I acknowledge that none of this would be possible without you.

Wael Mohamed
Kuantan, Pahang, Malaysia

To a special person I know, to Bassma Hajj-Ali, I dedicate this work.

Firas Kobeissy
Atlanta, GA, USA

Foreword

It was another usual busy day in the clinic, when my dear friend and colleague, Dr. El Hayek, approached me and asked if I could write the foreword for this book which focuses largely on the relationship between diet and mental health. For a moment, it felt like his invitation came as a wake-up call for me. For most of my colleagues working in mental healthcare, our day-to-day practice revolves around the traditional medical model of care, and though at the core of this is biopsychosocial approach to the care we strive to deliver, we don't seem to address the issue of diet or nutrition with the same rigour as we would for the likes of biochemical changes resulting from our prescribed medications. This area seems to attract a different, probably less superior regard, as compared to that for medication prescribing.

As we get along our clinical paths, and as we follow the approved guidelines that largely govern our clinical practice, we seem to lose touch with basics that underpin not only medical care, but also essential science that explains how the physiology, chemistry, and pathology of our bodies are all affected and governed by diet and nutrition. This is a branch of science related to the care of mental health which has been quite under-regarded so far.

You have in your hands a great compilation of the academic and professional experience and expertise of fellow colleagues from 14 different countries around the globe, in a worldwide collaboration to address diet and nutrition from different perspectives pertaining to mental health. The authors have scrutinised the body of evidence out there and have presented to the reader of this book robust evidence-based information upon which anyone interested in the ever-fascinating area of mental health, can find all necessary and up-to-date information on very interesting and topical-related topics. This book shall be a great source of information to guide many of us when considering advising our clients more professionally. It shall support our better understanding of this area and that interface.

I can't end my foreword without thanking Professor Kobeissy and Professor Mohamed enough for orchestrating the great work of that fine consortium of colleagues from around the world, to bring this valuable book to light, and a big thank you to all my fellow authors and co-authors. The impact of this work shall touch the

lives of many people. As the ancient Greek philosopher Pericles once said, “What you leave behind is not what is engraved in stone monuments, but what is woven into the lives of others”.

Erada Center for Treatment and Rehabilitation in Dubai Wael Foad
Dubai, United Arab Emirates

Preface

Exploring the intricacies of illness without books is like embarking on an uncertain voyage, while delving into books without the insights of patients is akin to remaining anchored to the shore.—Sir William Withey Gull (1816–1890)

Recently, the impact of nutrition and food intake has been highly investigated to study its impact on our brain function and development as it was shown that the diet we take will determine the outcome of certain brain disorders such as in brain injury and stroke. Along with its effects on cardiovascular diseases and cancer development, nutrition and diet have been shown to be involved in preserving our mental cognitive function and behavior. Recent studies have implicated that the development or exacerbation of certain neuropsychiatric disorders is related to an imbalance in our nutritional intake as observed in the development of obsessive-compulsive disorder (OCD), bipolar disorder, depression, and schizophrenia.

These findings have been driven by the revolutionary application of different "omics" fields and their application to studying the central nervous system (CNS) which broadened our understanding of fundamental neurobiological processes and has enabled the identification of proteins and pathways related to the complex molecular mechanisms underlying various diseases of the CNS. In fact, among these disciplines is the field of proteomics which has a subdiscipline of "Psychoproteomics" that evaluates the role of protein alterations in neuropsychiatric disorders aiming to identify biomarkers of such disorders. Furthermore, the fields of metabolomics and microbiome assessment have emerged to study the role of gut serotonin secretion and how it is implicated by "good" bacteria contributing to our sleep cycle, moods, and pain. Surveying the literature, we have noticed that there is a huge knowledge gap that discusses psychiatric health and the role of nutrition in modulating their outcomes. We are not implying that changes to our daily diet may be an alternative substitute for mental health intervention such as medication or psychoanalysis; however, we would like to highlight the role of a healthy diet and sound nutrition in alleviating certain psychiatric symptoms. Coming from a background of neuropsychiatric health research, the editors (Drs. Mohamed and Kobeissy) have decided to collaborate with other colleagues with expertise in the areas of psychiatric disorders and nutrition to address these knowledge gaps.

Overall, this new book provides updated and novel concepts in the field of psychiatry and its relation to food intake. The new compilation will be of high interest among researchers and clinical scientists involved in psychiatry, nutrition, and biochemistry.

Finally, we thank all the authors for their significant efforts in contributing such excellent chapters for this new edition. We are also sincerely grateful to each author for their patience during the compilation and final editing of this book.

Kuantan, Pahang, Malaysia — Wael Mohamed
Atlanta, GA, USA — Firas Kobeissy

Acknowledgments

First, we would like to express our great appreciation for all the authors who contributed to this timely project. The high level of devotion and dedication between the authors and editors made writing this book an enjoyable journey. In addition, we also extend our gratefulness to the authors who are in the fields of medical psychiatry and neuropsychiatric research for delivering years of their experience and work in different areas of psychiatric disorders to deliver such an elegant piece of work. The herein-discussed topics are of great value in the areas of nutrition, psychiatry, neurological disorders, and neurodegeneration. Finally, we would like to thank the encouragement of many of our friends and colleagues for their unconditional love, encouragement, and inspiration throughout the endeavor of the project.

Thank You

Wael Mohamed
Firas Kobeissy

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Wael Mohamed a Physician Neuroscientist, earned his Ph.D. from PSU, USA, and presently holds the position of Professor Madya at IIUM Medical School, Malaysia. With over 150 speaking engagements both domestically and internationally, Dr. Mohamed is a seasoned lecturer. He has authored more than 100 peer-reviewed papers in the field of Neuroscience/Psychiatry, boasting an h-index of 22. Additionally, he serves as an editor for several international Journals, having contributed to numerous journal special issues focusing on brain disorders. Furthermore, he is involved in editing several neuroscience books with several publishers. Dr. Mohamed has received research grants from esteemed national and international organizations including IBRO, ISN, MJF, STDF, FRGS, and INDO-ASEAN, totaling half a million US dollars in research funding. He is also the founder of the AfrAbia-PD-Genomic Consortium (AA-PD-GC).

Firas Kobeissy, PhD is a Professor of Neuroscience at the Department of Neurobiology, Neuroscience Institute Morehouse School of Medicine, Atlanta, GA, USA. Dr. Kobeissy serves as the Associate Director for the Center for Neurotrauma, Multiomics & Biomarkers (CNMB). Dr. Kobeissy obtained his Ph.D. from the University of Florida in the field of Neuroscience with a focus on brain injury biomarkers under the supervision of Drs. Ron Hayes and Kevin Wang. He obtained his Master's degree from the American University of Beirut, Beirut, Lebanon. His research spans utilizing different Multi-Omics applications related to brain injury models. Dr. Kobeissy has authored more than 300 articles, reviews, and book chapters along with two patents. He is the editor of nine books; these books involve brain injury, biomarker, and proteomics research. Dr. Kobeissy has served on several national and international grant review panels including the NSF, NIH, DoD, and the Department of Veteran Affairs. He served as the past president of the International Brain Research Organization—MENA chapter (2020–2023).

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Part I
Neurobiological Aspects of Psychiatric Disorders

Chapter 1
Neuroanatomy and Neuropathology of Psychiatry Disorders

Abayomi Oyeyemi Ajagbe, Michael Kunle Ajenikoko, and Abel Yashim Solomon

Abstract This comprehensive exploration delves into the intricate landscape of neuroanatomy and neuropathology in psychiatric disorders. The discussion synthesizes key findings from neuroimaging studies and research elucidating structural alterations in various mental illnesses, emphasizing the interplay between biological mechanisms, neuroplasticity, genetics, and environmental factors contributing to these changes. Integrating neuroanatomical insights into psychiatric diagnostics and treatment strategies offers promising avenues for precision medicine approaches, enabling targeted interventions tailored to individual neurobiological profiles. The significance of studying brain structure in advancing psychiatric care is underscored, highlighting the potential for innovative therapeutic interventions and the imperative need for ongoing research focusing on multimodal imaging, longitudinal assessments, and deeper investigations into the dynamic nature of neuroanatomical alterations. Emphasizing the clinical implications and future directions, this exploration underscores the pivotal role of understanding brain structure in shaping the landscape of mental health care, offering a foundation for improved patient outcomes and advancements in the field.

Keywords Neuroanatomy · Neuropathology · Psychiatric disorders · Neuroimaging · Neurostimulation

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1.1 Introduction to Neuroanatomy and Neuropathology in Psychiatry

Understanding the intricate relationship between neuroanatomy, neuropathology, and psychiatric disorders has become an imperative aspect in the field of mental health research (ENIGMA Bipolar Disorder Working Group et al. 2018; Goodkind et al. 2015). The convergence of neuroscience and psychiatry has unveiled remarkable insights into the structural underpinnings of various psychiatric conditions, shedding light on the neural substrates involved in mood regulation, cognition, and emotional processing (Decety and Moriguchi 2007; Malhi et al. 2015; Schumann et al. 2014).

Neuroanatomy, the study of the structure and organization of the nervous system, plays a pivotal role in delineating the neural basis of psychiatric illnesses (Blond et al. 2012; Vago et al. 2011). Concurrently, neuropathology investigates the structural and functional changes in the nervous system associated with disease states, offering critical insights into the pathological mechanisms underlying psychiatric disorders (Lucassen et al. 2014; Lyketsos et al. 2007).

Research conducted over recent decades has elucidated specific neuroanatomical alterations associated with diverse psychiatric conditions (Gong et al. 2019; Lui et al. 2016). For instance, studies employing advanced neuroimaging techniques have highlighted aberrations in key brain regions implicated in mood disorders, such as the prefrontal cortex, limbic system (including the amygdala and hippocampus), basal ganglia, and thalamus (ENIGMA Bipolar Disorder Working Group et al. 2018; Ng et al. 2009; Phillips and Swartz 2014). Such findings have not only contributed to unraveling the neural circuitry underlying these disorders but have also paved the way for novel diagnostic and therapeutic strategies.

The intricate interplay between genetic predisposition, environmental influences, and neurodevelopmental factors shapes the neuroanatomical architecture and contributes to the manifestation of psychiatric disorders (Akdeniz et al. 2014).

This chapter seeks to explore these multifaceted aspects, considering the pathophysiological mechanisms that underlie neuroanatomical changes observed in psychiatric conditions. Moreover, in the context of nutritional psychiatry, understanding the influence of diet and nutrients on brain structure and function is gaining prominence. Emerging evidence suggests a potential link between dietary patterns and neuroanatomical alterations in mental health disorders, emphasizing the significance of nutrition as a modifiable factor influencing brain health.

As we delve deeper into the neuroanatomy and neuropathology of psychiatric disorders, this chapter aims to synthesize existing knowledge while highlighting the gaps in understanding, thereby paving the way for future research directions in this evolving field.

Understanding brain structure is paramount in unraveling the complex underpinnings of mental health disorders. The brain's structural organization plays a fundamental role in shaping human behavior, cognition, emotions, and overall mental

well-being (Goodkind et al. 2015). Here are key points outlining the significance of comprehending brain structure concerning mental health:

Neural basis of mental health disorders: Brain structure forms the foundation for understanding the neural basis of mental health disorders (Schumann et al. 2014). Variations or alterations in specific brain regions, neural circuits, and connectivity patterns are often associated with various psychiatric conditions (Segal et al. 2023). For instance, structural changes in the prefrontal cortex, hippocampus, amygdala, and other regions have been linked to conditions like depression, anxiety, bipolar disorder, and schizophrenia.

Insights into cognitive and emotional functions: Different brain regions have specialized functions related to cognition, emotion regulation, memory, decision-making, and social interactions (Dehghani et al. 2023). Understanding how structural variations impact these functions helps elucidate the mechanisms underlying mental health disorders. For instance, changes in the amygdala's size or activity can affect emotional processing, potentially contributing to anxiety or mood disorders.

Advancements in neuroimaging techniques: Technological advancements in neuroimaging, such as magnetic resonance imaging (MRI), functional magnetic resonance imaging (fMRI), diffusion tensor imaging (DTI), and positron emission tomography (PET) scans, have enabled researchers to visualize and analyze brain structure and function non-invasively (Annavarapu et al. 2019; Goodkind et al. 2015; Yen et al. 2023). These tools allow for the identification of structural abnormalities or differences in individuals with psychiatric disorders compared to healthy individuals, offering valuable insights into the neurobiology of mental illnesses.

Personalized medicine and treatment approaches: Understanding individual variations in brain structure could pave the way for personalized medicine in mental health (Bora and Pantelis 2015; Schumann et al. 2014). It can assist clinicians in tailoring treatments based on an individual's neuroanatomical profile, leading to more targeted interventions and better treatment outcomes.

Early detection and intervention: Detecting structural changes in the brain associated with mental health conditions may enable early identification and intervention (Jiang et al. 2022). Early intervention is crucial in preventing the progression of certain disorders or mitigating their impact on an individual's life.

Research and therapeutic development: Research focusing on brain structure in mental health provides a foundation for developing novel therapeutic approaches (Goodkind et al. 2015). Insights gained from studying neuroanatomy and neuropathology contribute to the development of new medications, therapies, and interventions that target specific brain regions or neural circuits affected by psychiatric disorders.

In summary, comprehending brain structure is a cornerstone in addressing the complexities of mental health disorders (Bora and Pantelis 2015). It offers a crucial framework for research, diagnosis, treatment, and the development of interventions aimed at improving the lives of individuals affected by psychiatric conditions.

1.2 Depression

Depression, a complex and debilitating mental health disorder, is intimately associated with alterations in brain structure and function (Zhang et al. 2018). Neuroimaging studies have revealed distinct neuroanatomical changes in individuals affected by depression, offering critical insights into the neural underpinnings of this condition (Zhang et al. 2018).

1.2.1 Neuroanatomical Alterations Associated with Depression

Depression is characterized by significant neuroanatomical alterations observable through various neuroimaging techniques (Goodkind et al. 2015). Studies utilizing MRI and other imaging modalities consistently indicate structural changes in specific brain areas among individuals with depression (Han and Ham 2021). These alterations include reductions in gray matter volume, disruptions in white matter integrity, and aberrant neural connectivity patterns that correspond to depressive symptoms (Grieve et al. 2013; Smagula and Aizenstein 2016).

Notably, reduced hippocampal volume and altered amygdala function are among the most extensively studied neuroanatomical changes in depression (Hamilton et al. 2008; Yao et al. 2020). The hippocampus, known for its role in memory and emotion regulation, often exhibits reduced volume in individuals experiencing depressive episodes (Malykhin et al. 2010; Videbech 2004). Concurrently, the amygdala, a key component of emotional processing, tends to show heightened activation and structural changes associated with altered emotional responses in depression (Arnone et al. 2012; Park et al. 2019).

1. *Prefrontal cortex*
   The prefrontal cortex, encompassing the dorsolateral prefrontal cortex (DLPFC) and ventromedial prefrontal cortex (VMPFC), exhibits structural and functional abnormalities in depression (Goodkind et al. 2015). Disruptions in these areas are linked to impaired executive functions, emotional regulation deficits, and altered decision-making commonly observed in individuals with depression.
2. *Limbic system (amygdala and hippocampus)*
   Dysregulation within the limbic system, including the amygdala and hippocampus, contributes significantly to the emotional disturbances characteristic of depression (He et al. 2020). Altered amygdala reactivity and decreased hippocampal volume are closely associated with heightened emotional responses, impaired memory, and altered stress processing in depressive states (Belleau et al. 2019; Roddy et al. 2021).
3. *Anterior cingulate cortex (ACC) and insula*
   Structural and functional changes in the anterior cingulate cortex (ACC) and insular cortex are observed in depression (Goodkind et al. 2015; Maywald et al.

2022). These alterations are linked to disruptions in emotional regulation, self-referential thinking, and altered perception of bodily sensations, contributing to the subjective experiences of depression (Maywald et al. 2022).

Understanding these neuroanatomical changes in depression provides a crucial framework for elucidating the neural basis of depressive symptoms (Schmaal et al. 2020). Such insights offer promising avenues for targeted interventions and treatment approaches aimed at modulating specific brain regions or neural circuits affected in depression. Integrating neuroanatomical research with clinical practice holds the potential for more precise diagnostic tools and personalized therapeutic strategies to alleviate the burden of depression on affected individuals.

1.3 Anxiety Disorders

Anxiety disorders, encompassing various conditions such as generalized anxiety disorder (GAD), panic disorder, social anxiety disorder, and others, are closely associated with distinctive neuropathological correlations and alterations in specific brain regions contributing to the manifestation of anxiety symptoms (Shin and Liberzon 2010).

1.3.1 Neuroanatomical Changes in Anxiety Disorder

1. *Amygdala*: The amygdala plays a pivotal role in processing emotions, particularly fear and threat detection (Adolphs 2008; Fossati 2012). Altered amygdala reactivity and connectivity are consistent findings across various anxiety disorders, contributing to heightened emotional responses and exaggerated fear perception (Forster et al. 2012).
2. *Prefrontal cortex*: Structural and functional abnormalities in the prefrontal cortex, including the dorsomedial prefrontal cortex (DMPFC) and anterior cingulate cortex (ACC), are implicated in anxiety disorders (Santos et al. 2019; Shin and Liberzon 2010). Disruptions in these regions affect emotional regulation, attentional control, and fear extinction processes, exacerbating anxiety symptoms.
3. *Insular cortex*: The insula is involved in interoception and emotional awareness (Gogolla 2017). Changes in the insular cortex are associated with altered bodily sensations and emotional processing, contributing to the somatic symptoms and heightened self-awareness seen in anxiety disorders (Gogolla 2017; Grossi et al. 2017; Strawn et al. 2015).

1.3.2 Neuropathological Correlations with Different Anxiety Disorders

1. *Generalized anxiety disorder (GAD)*: Neuroimaging studies indicate alterations in the amygdala, prefrontal cortex, and insula in individuals diagnosed with GAD (Madonna et al. 2019; Kolesar et al. 2019). These structural and functional changes are associated with heightened fear responses, emotional dysregulation, and exaggerated worry, core features of GAD.
2. *Panic disorder*: Distinct neural alterations in the amygdala, hippocampus, and brainstem regions have been observed in individuals with panic disorder (Shin and Liberzon 2010). Aberrations in these areas contribute to increased threat perception, altered fear conditioning, and dysfunction in the brain's fear circuitry, culminating in panic attacks.
3. *Social anxiety disorder (SAD)*: Structural changes in the amygdala, prefrontal cortex, and insular cortex are commonly reported in individuals with SAD. Dysregulation in these brain regions underlies heightened social threat perception, fear of negative evaluation, and difficulties in social interactions characteristic of SAD.

Understanding the neuropathological correlations and affected brain regions in anxiety disorders provides critical insights into the underlying neural mechanisms driving anxiety symptoms. These findings have implications for targeted interventions aimed at modulating specific neural circuits to alleviate the burden of anxiety and improve the effectiveness of therapeutic interventions.

1.4 Bipolar Disorder

Bipolar disorder is a complex mood disorder characterized by recurrent episodes of mania, hypomania, and depression, with significant neuroanatomical implications that underlie its symptomatology (ENIGMA Bipolar Disorder Working Group et al. 2018; Strakowski et al. 2012).

BD is also known as "manic depression" because it is marked by high emotional states that last days to weeks and include manic/hypomanic (abnormally elated or irritated) or depressed (sad) episodes (Franchini et al. 2022). BD frequently manifests and is diagnosed during adolescence, when there is a shift in the processing of emotion and cognition from earlier developing subcortical gray regions to increased use of prefrontal brain structures, a time when the brain may be especially vulnerable to developmental neuropathologies (Bi et al. 2022; Emsell and McDonald 2009; Lim et al. 2013).

1.4.1 Neuroanatomical Changes Observed in Bipolar Disorder

Neuroimaging studies have revealed substantial neuroanatomical alterations in individuals diagnosed with bipolar disorder (BD) (Emsell and McDonald 2009; Houenou et al. 2011). Structural neuroimaging findings consistently report volumetric alterations and disruptions in gray and white matter integrity, particularly in brain regions associated with emotional regulation and mood control (Gray et al. 2020; Strakowski et al. 2012).

1. *Prefrontal cortex*: The prefrontal cortex, including the dorsolateral prefrontal cortex (DLPFC) and ventromedial prefrontal cortex (VMPFC), exhibits structural abnormalities in individuals with BD (ENIGMA Bipolar Disorder Working Group et al. 2018; Guo et al. 2021). These alterations contribute to executive function deficits, emotional dysregulation, and impaired decision-making observed during mood episodes (Guo et al. 2021).
2. *Amygdala and hippocampus*: Studies indicate variations in amygdala and hippocampal volumes in BD, impacting emotional processing, memory, and stress responses (Blumberg et al. 2003; Cao et al. 2016). Dysregulation in these limbic structures is associated with emotional intensity and affective instability observed in bipolar disorder (Henry 2012; Nabulsi et al. 2020; Townsend and Altshuler 2012).

1.4.1.1 Impacted Brain Structures Contributing to Mood Disturbances

1. *Limbic system dysfunction*: The dysregulation within the limbic system, particularly involving the amygdala and hippocampus, contributes significantly to mood disturbances in bipolar disorder (Blond et al. 2012; ENIGMA Bipolar Disorder Working Group et al. 2018; Townsend and Altshuler 2012). Altered functioning and connectivity in these areas are linked to emotional dysregulation, increased reactivity to emotional stimuli, and the oscillation between manic and depressive states (Blond et al. 2012; Townsend and Altshuler 2012).
2. *Prefrontal cortical dysfunction*: Abnormalities in the prefrontal cortex, affecting emotion regulation and cognitive control, contribute to mood instability and the inability to modulate emotional responses characteristic of BD (Cao et al. 2016; Green et al. 2007; Sankar et al. 2021). Dysfunction in this region plays a crucial role in the transition between manic and depressive episodes (Wei et al. 2017).

1.4.2 The Neuropathology of BD

Bipolar disorder (BD) lacks the diagnostic neuropathology that characterizes and identifies the dementias, like other "functional" mental diseases, although this does not imply that BD lacks morphological correlations (Harrison et al. 2020). Studies

using magnetic resonance imaging (MRI) reveal subtle but significant variations in the sizes of various brain regions, including smaller hippocampus, amygdala, and thalamus, as well as thinner cortical layers (Harrison et al. 2020). White matter declines are also supported by more and more research (Harrison et al. 2020). Although results have been inconsistent, postmortem neuropathological examinations have been scarce, and few research have looked at at-risk people, or early-stage BD, or conducted longitudinal studies, imaging studies largely support the idea that BD has a neurodevelopmental genesis (O'Shea and McInnis 2016). Imaging studies and meta-analyses of them have consistently found the following abnormalities in the BD brain: ventricular enlargement males with BD had smaller corpus callosums, lower prefrontal white matter volumes, larger cerebellar vermis volumes, and smaller prefrontal cortical areas (O'Shea and McInnis 2016).

Bipolar disorder's neural basis involves intricate alterations in brain structures, particularly in the prefrontal cortex and limbic system, contributing to mood disturbances and fluctuating emotional states observed in affected individuals. Understanding these neuroanatomical changes offers insights into targeted interventions aimed at modulating specific brain regions to manage mood swings and improve the overall quality of life for individuals with bipolar disorder.

1.5 Schizophrenia

Schizophrenia is a severe and chronic mental disorder characterized by disruptions in thought processes, perceptions, emotions, and behavior. The neural basis of schizophrenia involves multifaceted neuropathological aspects and alterations in specific brain structures and neural pathways (Baldaçara et al. 2008; Howes and Kapur 2009; Van Erp et al. 2018).

1.5.1 Brain Structure Alterations and Neural Pathways Linked to Schizophrenia

1. *Prefrontal cortex dysfunction*: Structural and functional abnormalities in the prefrontal cortex, including the dorsolateral prefrontal cortex (DLPFC), are prominent in schizophrenia (Meyer-Lindenberg et al. 2005; Smucny et al. 2022; Van Erp et al. 2018). Disruptions in this region are associated with impaired executive functions, decision-making, and working memory deficits observed in individuals with schizophrenia.
2. *Hippocampus and limbic system*: Alterations in the hippocampus and limbic system are prevalent in schizophrenia, contributing to deficits in memory, emotional regulation, and disturbances in the integration of sensory information (Boyer et al. 2007; Harrisberger et al. 2016; Howes and Kapur 2009). These changes are

linked to the hallucinations and emotional dysregulation characteristic of the disorder.

1.5.2 Neuropathological Aspects Associated with Schizophrenia

Neuropathological studies of schizophrenia reveal a spectrum of abnormalities encompassing alterations in brain morphology, neurochemistry, and synaptic connectivity (Coyle et al. 2020; Van Erp et al. 2018). These include:

1. *Cortical abnormalities*: Studies consistently report alterations in cortical thickness, reduced gray matter volume, and disruptions in the parietal, temporal, and frontal cortices among individuals with schizophrenia (Schultz et al. 2010; Van Erp et al. 2018; Xiao et al. 2015). These structural changes contribute to cognitive deficits and disruptions in sensory processing observed in schizophrenia.
2. *Dysregulated neurotransmission*: Dysfunctions in neurotransmitter systems, particularly dopamine and glutamate, are implicated in the pathophysiology of schizophrenia (Goff and Coyle 2001; Howes and Kapur 2009; McCutcheon et al. 2020; Meisenzahl et al. 2007). Dysregulation of these neurotransmitters contributes to altered synaptic transmission, leading to cognitive impairments and positive and negative symptoms of the disorder (McCutcheon et al. 2020).

Understanding the neuropathological aspects and brain structure alterations associated with schizophrenia is crucial for unraveling the complexities of this disorder. Insights into the neural pathways linked to schizophrenia offer opportunities for the development of targeted interventions aimed at ameliorating cognitive deficits, managing symptoms, and improving functional outcomes for individuals affected by schizophrenia.

Several neuroanatomical features are shared among various psychiatric disorders, suggesting common underlying mechanisms:

1. *Prefrontal cortex alterations*: Studies indicate structural and functional abnormalities in the prefrontal cortex across multiple psychiatric illnesses, including depression, bipolar disorder, schizophrenia, and anxiety disorders (Goodkind et al. 2015; Hibar et al. 2018). Dysregulation in this region contributes to impairments in executive functions, emotion regulation, and cognitive control observed across these conditions.
2. *Limbic system involvement*: Aberrations in the limbic system, particularly the amygdala and hippocampus, are commonly implicated in mood disorders (depression and bipolar disorder), anxiety disorders, and schizophrenia (Van Erp et al. 2018). Altered emotional processing, memory disturbances, and stress response abnormalities are shared features associated with these conditions.

While there are shared neuroanatomical alterations, distinct neural patterns specific to each psychiatric disorder also exist:

1. *Dopaminergic system dysfunction in schizophrenia*: The dopamine hypothesis highlights the role of dopaminergic abnormalities, particularly in schizophrenia, contributing to positive symptoms such as hallucinations and delusions (Howes and Kapur 2009). This neural pattern is distinct and specific to schizophrenia.
2. *Glutamatergic dysregulation in mood disorders*: Studies emphasize the involvement of altered glutamatergic neurotransmission in mood disorders like depression and bipolar disorder (Maletic and Raison 2014; Yüksel and Öngür 2010). Dysfunctions in glutamate pathways contribute to mood disturbances and cognitive impairments unique to these conditions.

Certain brain regions and neural circuits exhibit overlap in their involvement across various psychiatric illnesses:

1. *Default mode network (DMN) dysfunction*: Disruptions in the DMN, including the medial prefrontal cortex and posterior cingulate cortex, are observed in depression, anxiety, and schizophrenia (Goodkind et al. 2015). Altered connectivity within the DMN is associated with impaired self-referential thinking and rumination, features seen across these conditions.
2. *Hypothalamic-pituitary-adrenal (HPA) axis dysregulation*: Abnormalities in the HPA axis, involved in stress response, are implicated in depression, anxiety, and some aspects of bipolar disorder (Jacobson 2014; Maletic and Raison 2014; Phillips et al. 2006). Dysregulated cortisol levels and altered stress responsiveness contribute to symptomatology in these disorders (Dziurkowska and Wesolowski 2021; Maletic and Raison 2014).

In summary, a comparative analysis of neuroanatomical features across psychiatric disorders reveals both shared commonalities and distinct neural patterns specific to each condition. Understanding these similarities and differences provides valuable insights into the heterogeneity and complexity of psychiatric illnesses, paving the way for more targeted diagnostic and therapeutic approaches tailored to individual neural profiles.

1.6 Neuroimaging Techniques and Findings

Neuroimaging methods serve as essential tools in investigating the neuroanatomy, neuropathology, and structural alterations associated with various psychiatric disorders. These techniques offer insights into the underlying neural correlates and provide valuable information aiding our understanding of the neurobiology of these conditions.

Structural MRI (magnetic resonance imaging): Structural MRI allows the visualization of brain structures and provides detailed anatomical information, enabling

researchers to examine alterations in gray matter volume, white matter integrity, and cortical thickness associated with psychiatric disorders (Goodkind et al. 2015).

Diffusion tensor imaging (DTI): DTI measures the diffusion of water molecules in the brain, allowing the assessment of white matter tracts' integrity and connectivity (Assaf and Pasternak 2008; Madden et al. 2012). It provides insights into abnormalities in neural connectivity observed in psychiatric conditions such as schizophrenia and mood disorders (Heng et al. 2010; Lim and Helpern 2002).

Functional MRI (fMRI): fMRI measures brain activity by detecting changes in blood flow. This technique helps identify alterations in functional connectivity, task-related activations, and resting-state networks, offering insights into the functional abnormalities associated with psychiatric disorders (ENIGMA Bipolar Disorder Working Group et al. 2018).

Neuroimaging studies have yielded significant findings elucidating structural alterations in various psychiatric disorders:

1. *Gray matter abnormalities*: Reduced gray matter volume or density in specific brain regions, including the prefrontal cortex, hippocampus, and amygdala, has been consistently observed across conditions like depression, schizophrenia, and bipolar disorder (Almeida et al. 2009; Bora et al. 2010).
2. *White matter disruptions*: Abnormalities in white matter integrity, as indicated by alterations in fractional anisotropy (FA) in DTI studies, have been reported in conditions such as schizophrenia, mood disorders, and anxiety disorders, suggesting disruptions in neural connectivity (Heng et al. 2010; Lee et al. 2020; Sagarwala and Nasrallah 2020).

Neuroimaging techniques have provided invaluable insights into the neurobiology of psychiatric conditions:

1. *Identification of neural circuitry involved*: Neuroimaging studies have identified specific brain circuits and networks implicated in various psychiatric disorders (Fornito and Bullmore 2012; McTeague et al. 2020). For instance, aberrations in the default mode network (DMN) and salience network have been associated with mood disturbances and cognitive deficits observed across conditions (Hua et al. 2019).
2. *Biomarkers and predictive measures*: Neuroimaging findings have contributed to the identification of potential biomarkers and predictive measures for diagnosing and predicting the course of psychiatric illnesses. These biomarkers aid in early detection and intervention strategies (Orrù et al. 2012; Walton et al. 2013).

1.7 Pathophysiological Mechanisms Underlying Neuroanatomical and Neuropathological Changes

Understanding the intricate pathophysiological mechanisms contributing to alterations in brain structure is crucial in deciphering the complexities of psychiatric disorders. These mechanisms encompass biological, neuroplasticity-related, and multifactorial influences involving genetics, environment, and developmental factors, influencing the neural architecture and functioning in these conditions.

1. *Neuroinflammation and oxidative stress*: Chronic neuroinflammation and increased oxidative stress contribute significantly to structural alterations in psychiatric disorders (Kim and Won 2017; Rossetti et al. 2020). Pro-inflammatory cytokines and reactive oxygen species disrupt synaptic plasticity, contributing to neuronal damage and aberrant neural connectivity observed in conditions like schizophrenia and mood disorders (De Bartolomeis et al. 2022; Murray et al. 2021; Nakagawa and Chiba 2015).
2. *Neurotransmitter imbalance*: Dysregulated neurotransmitter systems, such as dopamine, serotonin, glutamate, and GABA, influence brain structural changes in psychiatric illnesses (Delva and Stanwood 2021; Gold 2015). Imbalances in these neurotransmitters impact synaptic plasticity, neural circuitry, and neuronal survival, contributing to structural abnormalities seen in various disorders (Duman et al. 2019; Pralong 2002).

1.7.1 Factors Influencing Neuroplasticity and Structural Changes in Psychiatric Disorders

1. *Stress and cortisol dysregulation*: Prolonged stress and dysregulated cortisol levels exert profound effects on neuroplasticity and brain structure, particularly in stress-responsive regions like the hippocampus and prefrontal cortex (Gold 2015). These alterations impair synaptic plasticity and increase vulnerability to psychiatric conditions.
2. *Environmental factors*: Environmental influences, including early-life adversity, trauma, substance abuse, and socio-economic factors, significantly influence neuroplasticity and brain structure in psychiatric disorders (Qiu and Liu 2023; Tost et al. 2015). Adverse experiences during critical developmental periods can modify neural circuits, impacting brain development and increasing susceptibility to mental illnesses.

1.7.2 Genetic, Environmental, and Developmental Influences on Neuroanatomy in Mental Illnesses

1. *Genetic contributions*: Genetic factors contribute substantially to brain structure and susceptibility to psychiatric disorders (Burmeister et al. 2008; Kendler 2001; Smoller et al. 2019). Variations in genes related to neurodevelopmental processes, synaptic function, and neurotransmitter systems influence brain morphology and confer risk for mental illnesses.
2. *Developmental trajectories*: Neuroanatomical alterations in psychiatric disorders often originate from disrupted developmental processes during critical periods (Marco et al. 2011; Marín 2016). Perturbations in neurodevelopment, including abnormalities in neurogenesis, neuronal migration, and synaptic pruning, contribute to persistent structural changes observed in these conditions.

The pathophysiological mechanisms underlying neuroanatomical and neuropathological changes in psychiatric disorders represent a complex interplay of biological, environmental, and genetic factors influencing brain structure and function. Understanding these mechanisms provides a comprehensive framework for elucidating the etiology and progression of psychiatric conditions, potentially guiding the development of targeted therapeutic interventions.

1.8 Clinical Implications and Future Directions

Integrating neuroanatomical knowledge into psychiatric diagnostics and treatment is paramount for advancing clinical practices. Understanding the neural underpinnings of psychiatric disorders holds promise for innovative therapeutic interventions and identifies future research directions.

1.8.1 Enhanced Diagnostic Precision

Neuroimaging-based biomarkers derived from neuroanatomical alterations aid in objective and accurate diagnostic procedures (Fu and Costafreda 2013). Imaging markers provide additional validity and objectivity in diagnosing various psychiatric conditions, allowing for more precise classification and personalized treatment strategies (Abi-Dargham and Horga 2016).

1.8.2 Potential Therapeutic Interventions Targeting Neuroanatomical and Neuropathological Alterations

Neurostimulation techniques: Non-invasive brain stimulation techniques, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), modulate neural circuits and show promise in treating psychiatric disorders by targeting specific brain regions (Sparing and Mottaghy 2008).

Neuroplasticity-based interventions: Interventions promoting neuroplasticity, including cognitive training, mindfulness-based therapies, and physical exercise, have shown beneficial effects on brain structure and function in psychiatric populations (Keshavan et al. 2014). These interventions foster adaptive changes in neural networks, potentially ameliorating structural abnormalities.

Future research directions aiming to deepen the understanding of neuroanatomy in psychiatric disorders involve:

1. *Multimodal imaging approaches*: Integrating multiple neuroimaging modalities, such as combining structural MRI with functional imaging techniques like fMRI or PET, offers a comprehensive understanding of the relationship between brain structure and function in psychiatric illnesses (McGuire and Matsumoto 2004).
2. *Longitudinal studies*: Longitudinal investigations tracking neuroanatomical changes over time are crucial to elucidate the dynamic nature of structural alterations and their associations with disease progression, treatment response, and functional outcomes (Dietsche et al. 2017).

The integration of neuroanatomical knowledge into psychiatric diagnostics and treatment holds significant promise for improving clinical practices. Targeted therapeutic interventions leveraging neuroimaging-based markers and ongoing research endeavors exploring advanced imaging techniques and longitudinal assessments pave the way for a more nuanced understanding of neuroanatomy in psychiatric disorders, potentially transforming patient care.

1.9 Conclusion

The exploration of neuroanatomy and neuropathology in psychiatric disorders unveils intricate insights into the underlying biological substrates of mental illnesses, providing a foundation for advancements in psychiatric care and guiding future research endeavors.

1.9.1 Summary of Key Points Discussed Regarding Neuroanatomy and Neuropathology in Psychiatric Disorders

Throughout this exploration:

1. *Neuroanatomical alterations*: Evidence has highlighted consistent neuroanatomical alterations, including changes in gray matter volume, white matter integrity, and alterations in specific brain regions such as the prefrontal cortex, limbic system, and hippocampus across various psychiatric disorders (Goodkind et al. 2015; Van Erp et al. 2018).
2. *Pathophysiological mechanisms*: Biological factors, neurotransmitter imbalances, environmental influences, and genetic predispositions contribute significantly to structural changes observed in psychiatric conditions (Howes and Kapur 2009; Teicher et al. 2016).
3. *Clinical implications*: Integrating neuroanatomical knowledge into psychiatric diagnostics and treatments offers opportunities for enhanced precision in diagnostics, targeted therapeutic interventions, and personalized patient care (McEwen et al. 2016).

The profound insights gained from exploring neuroanatomy and neuropathology in psychiatric disorders underscore the critical role of brain structure in shaping the landscape of mental health. By leveraging these insights, clinicians and researchers can stride toward more informed and targeted approaches in psychiatric care, ultimately fostering improved well-being for individuals affected by these complex conditions.

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Chapter 2
Biochemical and Neuropharmacology of Psychiatric Disorders

Youssef K. Ghallab and Omnia S. Elassal

Abstract Psychiatric disorders represent a significant socioeconomic and healthcare burden worldwide. Of these, schizophrenia, bipolar disorder, major depressive disorder, and anxiety are among the most prevalent. Unfortunately, diagnosis remains problematic and largely complicated by the lack of disease-specific biomarkers. Accordingly, much research has focused on elucidating these conditions to understand underlying pathophysiology more fully and potentially identify biomarkers, especially those of early-stage disease. This chapter dives deep into how our brains work, how imbalances in brain chemicals can lead to mental health issues like depression and anxiety, and how medications can help restore that balance. It explores the connections between what we eat and how our brains function, showing how nutrition can play a role in managing mental health conditions. It also talks about the challenges in diagnosing these conditions since there aren't specific tests for them yet. The chapter gives practical advice for doctors on using genetics to choose the best medications for each person and how to monitor those medications to keep patients safe. It delves into the intricate neurochemical basis of psychiatric disorders, elucidating the pivotal roles played by neurotransmitters in mental health while unveiling the implications of imbalances in various psychiatric conditions. Within the exploration of major psychiatric disorders, the chapter provides an in-depth analysis of the intricate biological mechanisms governing depression, anxiety disorders, schizophrenia, and bipolar disorder. Furthermore, it casts a spotlight on the pivotal impact of nutrition on neurochemistry, scrutinizing the intricate interplay between dietary patterns, micronutrients, and the delicate balance of neurotransmitter function. Beyond this exploration, the chapter extends into uncharted territories,

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delving into emerging research horizons and illuminating potential synergies between neuropharmacological and nutritional approaches, heralding a new paradigm for advancing psychiatric care and illuminating novel pathways toward holistic well-being.

Keywords Neuropharmacology · Psychiatric disorders · Neurotransmitters · Biological mechanisms · Psychotropic medications · Nutrition · Neurochemical balance · Integrative approaches

2.1 Introduction to Neuropharmacology

Neuropharmacology is a fascinating and interdisciplinary scientific field that explores the impact of drugs on the central nervous system. It seeks to understand the intricate interplay between molecules and substances in the nervous system, with a particular focus on the reversible molecular interactions between receptors and ligands. With its roots in pharmacology, neuropharmacology covers the basics of agonism, antagonism, and affinity, delving deeper into molecular targets at the synapse, including ionotropic and metabotropic receptors (Zeise 2021).

Over the years, neuropharmacology has undergone significant transformations, with groundbreaking discoveries in psychotropic alkaloids, neuroleptics, and dopaminergic and serotonergic drugs. This field has also contributed significantly to the understanding of addiction and the intrinsic neural circuitry of reward and motivated behavior, where dopamine plays a vital role (Neuropharmacology 2023).

Despite impressive advancements, there are still challenges in the field, and areas of brain-based therapeutics, particularly in psychiatry, require further exploration. Nevertheless, neuropharmacology remains an essential field of scientific inquiry that has the potential to revolutionize our understanding of the central nervous system and develop new, more effective treatments for neurological and psychiatric disorders (Jain 2002).

Addiction is a complex disorder that is characterized by compulsive drug-seeking behavior despite negative consequences. It involves various neurobiological mechanisms that cause alterations in the brain's reward circuitry. The mesolimbic dopamine system, which is responsible for the pathway projecting from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) and other brain regions, plays a central role in reward processing and reinforcement learning. Dopamine is a key player in this reward pathway and is involved in mediating the reinforcing effects of drugs of abuse. Drugs such as cocaine, amphetamines, and opioids affect dopamine neurotransmission either directly or indirectly. They can enhance dopamine release or inhibit its reuptake, leading to an increase in synaptic dopamine levels within the NAc. This surge in dopamine transmission contributes to the intense euphoria or pleasure associated with drug use.

Chronic drug exposure induces changes in the reward circuitry, leading to alterations in dopamine signaling. Over time, these changes can result in tolerance, where

higher doses of the drug are needed to achieve the same effects, and in the development of addiction-related behaviors, including compulsive drug-seeking and drug-taking despite negative consequences. Neuropharmacological studies have elucidated various aspects of dopamine's role in addiction, including the involvement of specific dopamine receptor subtypes (such as D1 and D2 receptors) in mediating different facets of addictive behaviors. Moreover, the interactions between dopamine and other neurotransmitter systems (such as glutamate, serotonin, and endogenous opioids) further modulate the complex neurocircuitry underlying addiction.

Understanding the intricate interplay between drugs of abuse and the dopamine-mediated reward system is essential in developing targeted pharmacotherapies for addiction. Research into novel medications that can modulate dopamine signaling or alter the neuroplastic changes induced by chronic drug exposure holds promise for treating substance use disorders. The neuropharmacology of addiction continues to be an active area of research, aiming not only to elucidate the mechanisms underlying addictive behaviors but also to identify potential therapeutic interventions that could mitigate the devastating impact of substance abuse on individuals and society.

Neuropharmacology also plays a significant role in understanding neurodevelopmental disorders, such as autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD). Studies on neurotransmitter function and brain circuitry in these conditions are leading to new therapeutic approaches that can help manage symptoms and improve outcomes for affected individuals.

2.1.1 Understanding Neurotransmission

Neurotransmission is an intricate process that plays a crucial role in regulating various physiological and pathological functions in the brain. It involves the transmission of signals between neurons through chemical messengers known as neurotransmitters, which are responsible for regulating brain function. These chemical messengers can be classified into several categories, each with their unique properties and functions, including amino acids, amines, purines, gases, arachidonic acid derivatives, and peptides (Wang 2022). When a neurotransmitter is released, it binds to specific receptors located at pre- and postsynaptic sites. These receptors can be ionotropic or metabotropic, and they mediate the response of the neurotransmitter. Ionotropic receptors work quickly, involving ion channels that allow ions to flow in and out of the cell. Metabotropic receptors work slowly, involving intracellular signaling pathways that trigger a cascade of events in the cell (Pichai and Lakshmanan 2021).

The clustering of neurotransmitter receptors at synapses is not yet fully understood. However, research has shown that abnormalities in neurotransmitter systems can contribute to various brain disorders. For instance, abnormalities in dopamine and serotonin systems are linked to depression, anxiety, and addiction, while

abnormalities in glutamate and GABA systems are associated with schizophrenia and epilepsy (Uysal 2023).

Recent advancements in biosensors have allowed for the visualization of neurotransmitter dynamics with high resolution, aiding in the understanding of the role of neurotransmitters in behavior. For instance, dopamine release in the brain's reward center is associated with pleasure and motivation, while serotonin release in the prefrontal cortex is linked to mood regulation and impulse control. Neurotransmitters like dopamine and serotonin serve as key messengers in our brain, orchestrating a symphony of emotions and behaviors. Dopamine, celebrated as the herald of pleasure and motivation, dances within our brain's reward circuitry, driving us toward activities that bring joy and fulfillment. In contrast, serotonin reigns in the realm of emotional stability and impulse control, wielding its influence in the prefrontal cortex to modulate mood and temper impulsive urges. These intricate neurotransmitter dynamics form the bedrock of our mental landscape, shaping our experiences, motivations, and emotional equilibrium (Kubitschke and Masseck 2024).

Neurotransmitters stand as the messengers orchestrating our brain's intricate symphony, influencing our emotions, motivations, and behaviors. Their diverse functions, from dopamine's role in pleasure and motivation to serotonin's impact on mood regulation and impulse control, underscore the nuanced complexity of our mental landscape. The study of neurotransmission unveils critical insights into neurological disorders, linking abnormalities in specific neurotransmitter systems to conditions like depression, anxiety, schizophrenia, and addiction. Advancements in biosensor technology have illuminated these neurotransmitter dynamics, offering glimpses into their precise roles in shaping human behavior. As our understanding of these neurotransmitters deepens, it paves the way for innovative treatments and interventions, promising hope for individuals grappling with neurological conditions. These insights highlight the profound influence of neurotransmitters, like dopamine and serotonin, acting as pivotal messengers shaping our emotions, motivations, and overall mental balance within the intricate landscape of our brain. Exploring the depths of neurotransmission continues to be a frontier that holds immense potential, driving progress toward unraveling the mysteries of the brain and improving human well-being (Miller and Yeh 2017).

2.1.2 Overview of Brain Biochemistry

The brain's biochemistry is a fascinating and intricate system of molecular components that play a crucial role in the functioning of the central nervous system. One of its most vital components is neurotransmitters—chemical substances that facilitate communication between neurons. These neurotransmitters, including dopamine, serotonin, acetylcholine, and γ-aminobutyric acid (GABA), have a precise regulatory impact on neural circuits, influencing a wide range of cognitive, emotional, and physiological processes. Enzymatic pathways, such as tyrosine

hydroxylase for dopamine and tryptophan hydroxylase for serotonin, synthesize these neurotransmitters from precursor molecules. Upon release, these neurotransmitters interact with various receptors, including G protein-coupled receptors (GPCRs), ionotropic receptors, and metabotropic receptors, initiating signal transduction cascades that modulate synaptic transmission and neuronal excitability (Hajjawi 2014).

The homeostasis of neurotransmitter systems constitutes a fundamental determinant of cerebral function. Perturbations within these systems are implicated in various neuropathological conditions. For instance, the selective degeneration of dopaminergic neurons within the substantia nigra pars compacta heralds Parkinson's disease, characterized by motor impairments. Conversely, depressive disorders are associated with altered serotonin signaling or reduced serotonin levels, eliciting mood disturbances and cognitive impairments. Alzheimer's disease, marked by cognitive decline and memory deficits, manifests through the progressive loss of cholinergic neurons in the basal forebrain, precipitating diminished acetylcholine levels and neurodegeneration (Everett et al. 2023).

The energy requirements of the brain are closely intertwined with its function. Glucose, the primary energy source, powers neuronal activity and supports the creation of neurotransmitters. This emphasizes the close connection between maintaining energy balance and neurotransmission (Ryman et al. 2011). Advanced neuroimaging techniques, including functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) scans, have brought about a paradigm shift in our understanding of neural activity and complex neural networks. These cutting-edge technologies have enabled scientists to visualize brain function and neural activity in unprecedented detail, thereby advancing our knowledge of the brain's intricate workings (Ghosh and Smith 2011).

Molecular studies have revealed the underlying mechanisms of neurotransmitter dysregulation, paving the way for the development of targeted pharmacotherapies. These precision treatments, which include selective serotonin reuptake inhibitors (SSRIs) for depression and dopamine agonists for Parkinson's disease, specifically address imbalances in neurotransmitters, alleviate symptoms, and enhance the overall quality of life for patients. By utilizing these innovative approaches, researchers and healthcare professionals can gain a deeper understanding of the brain and its functions, ultimately leading to more effective treatments and improved outcomes for patients (Shill et al. 2012).

Understanding the molecular underpinnings of neurotransmitter systems also allows for the development of novel therapeutic strategies. For example, identifying specific genetic markers linked to neurotransmitter dysregulation can lead to personalized medicine approaches, where treatments are tailored to the individual's genetic profile. Additionally, exploring the role of neurotransmitters in neuroplasticity—the brain's ability to reorganize itself by forming new neural connections—can provide insights into rehabilitation strategies for brain injury and neurodegenerative diseases.

2.2 Neurochemical Basis of Psychiatric Disorders

Psychiatric disorders such as schizophrenia, major depressive disorder, bipolar disorder, and anxiety disorders are complex and multifaceted conditions that involve intricate interactions between genetic, epigenetic, and environmental factors. Their pathogenesis is influenced by hundreds of genes and numerous pathways, including DNA methylation, transcription, and splicing. Additionally, immune activation has been shown to play a role in the chronicity and treatment resistance of psychiatric disorders, with changes in immune molecules in the brain affecting neurotransmitter systems and stress hormones (Blokhin et al. 2020).

Furthermore, it has been discovered that the neurochemical basis of psychiatric disorders involves structural, chemical, and functional changes in the brain. For instance, folate deficiency and impaired folate transport to the brain have been linked to developmental and psychiatric disorders such as autism, epilepsy, and treatment-resistant depression. Studies have also shown that changes in neurotransmitter systems are extensively implicated in various psychiatric disorders (Ramaekers et al. 2016).

Neurotransmitters such as serotonin, dopamine, norepinephrine, GABA, glutamate, and acetylcholine serve as critical messengers in the intricate network of neural communication within the brain. Dysregulation or imbalance in these neurotransmitter systems has been linked to alterations in mood, sleep, appetite regulation, reward processing, motivation, motor function, heightened states of arousal and stress response, cognitive processes such as learning and memory, and neuromuscular control. These imbalances and dysregulations in neurotransmitter systems underscore the multifaceted nature of psychiatric disorders, which arise from a confluence of genetic predisposition, environmental factors, and neural circuitry abnormalities (Guidotti and Grayson 2011). To address the imbalances and dysregulations in neurotransmitter systems, pharmacological interventions targeting specific neurotransmitter systems have been developed to restore their balance and function. These interventions aim to ameliorate symptoms and offer potential avenues for therapeutic strategies in psychiatric care and treatment. Understanding the neurophysiological and molecular mechanisms underlying the neurochemical foundations of psychiatric disorders is crucial for identifying potential therapeutic targets and developing personalized treatments for these conditions. By focusing on specific neurotransmitter systems and their dysregulation and imbalances, we can work toward developing effective treatments for psychiatric disorders that address their multifaceted nature (Qian et al. 2022).

Advancements in genetic and molecular research have facilitated a deeper understanding of how neurotransmitter systems are altered in psychiatric disorders. This has led to the identification of novel biomarkers that can aid in the diagnosis and treatment of these conditions. For instance, variations in genes related to serotonin transporters have been associated with depression, while polymorphisms in dopamine receptor genes are linked to schizophrenia. Furthermore, integrating neurochemical research with neuroimaging techniques allows for the visualization of

neurotransmitter activity in real time, providing a more comprehensive understanding of how these systems operate in both healthy and diseased states. Techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) enable researchers to observe the dynamic changes in neurotransmitter levels and their impact on brain function and behavior.

2.2.1 Role of Neurotransmitters in Mental Health

Neurotransmitters play a crucial role in mental health by mediating signals between neurons. These chemical messengers are responsible for transmitting information across synapses, the gaps between neurons. Imbalances in neurotransmitters can lead to various mental disorders, such as depression, anxiety, and memory loss. Monitoring neurotransmitters and psychiatric medications is essential for diagnosing and treating mental illness (Gasmi et al. 2022).

Certain neuropeptides, such as oxytocin and vasopressin, also contribute to mental health by regulating social behavior, anxiety, and depression. Oxytocin, commonly known as the "love hormone," is released during social bonding and promotes feelings of trust, empathy, and relaxation. Vasopressin, on the other hand, is involved in regulating social behavior, aggression, and stress responses (Zamani et al. 2022). The intricate interplay of neurotransmitters forms the backbone of mental health regulation, impacting mood, cognition, behavior, and overall well-being. Serotonin, primarily found in the brain and the gut, plays a multifaceted role in regulating mood, sleep-wake cycles, appetite, and social behavior. Disruptions in serotonin signaling pathways, often associated with genetic predispositions or environmental triggers, have been extensively linked to mood disorders, such as major depressive disorder and various anxiety disorders.

Dopamine, crucial in the brain's reward and pleasure circuits, influences motivation, reward-seeking behavior, motor control, and executive functions. Dysfunctions in dopamine transmission are notably implicated in conditions such as schizophrenia, where excess dopamine activity is observed, as well as in Parkinson's disease, marked by dopamine deficiency (Hammock 2023).

Norepinephrine, a stress hormone and neurotransmitter, contributes significantly to the body's "fight or flight" response. It modulates attention, focus, mood, and arousal. Imbalances in norepinephrine levels are linked to mood disorders, including depression and anxiety, as well as to post-traumatic stress disorder (PTSD) (Romash et al. 2023).

GABA, the primary inhibitory neurotransmitter in the brain, exerts a calming effect by reducing neuronal excitability. Insufficient GABA activity is associated with anxiety disorders, panic attacks, and epilepsy. Glutamate, the most abundant excitatory neurotransmitter in the brain, plays a critical role in synaptic plasticity, learning, and memory formation. Disruptions in glutamate signaling have been implicated in conditions such as schizophrenia, anxiety disorders, and major depressive disorder (Blows 2000).

Acetylcholine, vital for cognitive functions such as memory, attention, and learning, undergoes alterations in neurodegenerative conditions, prominently in Alzheimer's disease. The intricate balance and interactions among these neurotransmitter systems are essential for maintaining mental health. Dysregulation, whether through genetic factors, environmental influences, or other neurological changes, can lead to the manifestation of psychiatric disorders (Blows 2000).

Pharmacological interventions often target these neurotransmitter systems to restore balance and alleviate symptoms associated with various mental health conditions, representing a crucial avenue in the management and treatment of psychiatric disorders. However, it is important to note that medication alone is not always sufficient, and psychotherapy and lifestyle changes may also be necessary for optimal outcomes (Hammock 2023).

2.3 Biological Mechanisms of Major Psychiatric Disorders

The development of major psychiatric disorders is a complex process involving various factors such as genetics, molecular processes, and oxidative and inflammation system deficits (Cao et al. 2022). Interestingly, sulforaphane (SFN), a dietary phytochemical, has shown promising results in clinical trials for major mental disorders. It helps in upregulating antioxidants, protecting neurons against oxidative damage, and reducing inflammatory response (Zheng et al. 2022). Research has revealed that several genes and pathways are involved in the pathogenesis of psychiatric illnesses such as schizophrenia, major depressive disorder, and alcohol use disorder. These disorders are genetically interrelated and can be categorized based on their general psychopathology (Blokhin et al. 2020). Cross-scale and multi-omics approaches combining genes and imaging have provided valuable insights into the structural and functional brain changes associated with these disorders, offering potential biomarkers for diagnosis and prognosis. Parental loss in childhood has been identified as a risk factor for mental disorders, affecting stress response and emotion-related behaviors through neurobiological changes (Fan et al. 2023).

The biological mechanisms underlying major psychiatric disorders involve a complex interplay of several factors, including genetic predispositions, fluctuations of neurotransmitters such as serotonin and dopamine, brain structure and function alterations revealed through neuroimaging, and the influence of environmental triggers such as stress, trauma, or substance abuse. Additionally, epigenetic modifications, immune system dysregulation, and neurodevelopmental anomalies during critical periods also contribute significantly (Zanta et al. 2023). The current understanding highlights the disruption in neural circuits and networks rather than isolated brain abnormalities. The intricate interactions among genetic, neurobiological, and environmental factors underscore the complexity of psychiatric disorders, emphasizing the need to integrate this knowledge for developing more effective

treatments and interventions customized to address the diverse aspects of these conditions (Kim et al. 2019).

Further complicating the landscape of psychiatric disorders is the role of neuroinflammation and oxidative stress. Chronic inflammation and oxidative damage have been linked to the pathophysiology of disorders like depression and schizophrenia. These conditions are often accompanied by elevated levels of pro-inflammatory cytokines and reactive oxygen species, which can exacerbate neuronal damage and disrupt neurotransmitter function. Sulforaphane, by boosting the body's antioxidant defenses and reducing inflammation, presents a promising therapeutic avenue. Moreover, the impact of environmental factors such as early-life stress and trauma cannot be overstated. These experiences can lead to long-lasting changes in brain structure and function, altering stress response systems and increasing susceptibility to psychiatric disorders later in life. Neuroimaging studies have shown that individuals who experienced significant early-life stress exhibit changes in brain areas involved in emotion regulation, such as the hippocampus and prefrontal cortex. Epigenetic modifications, which involve changes in gene expression without altering the DNA sequence, also play a crucial role in the development of psychiatric disorders. These modifications can be influenced by environmental factors and contribute to the heritability and variability of these conditions. For instance, DNA methylation patterns have been found to differ significantly in individuals with psychiatric disorders compared to healthy controls, suggesting that these epigenetic changes may be involved in the disease process.

2.3.1 Depression: Neurochemical Underpinnings

Depression is a multifaceted disorder that involves imbalances in neurochemicals. Affected individuals often exhibit irregular biological pathways, including inflammation and disrupted neuroendocrine signaling. These pathways may explain the connection between depression and cardiometabolic conditions (Corrigan et al. 2023). The immune and endocrine systems are involved in driving these changes, with stress hormones, immune cells, and soluble mediators of immunity interacting within the nervous system. The imbalance of neurotransmitters, especially 5-hydroxytryptamine (5-HT), is implicated in the development of depression, and the dorsal raphe nucleus (DRN) plays an integral role (Noworyta et al. 2021). Depression involves dysregulation in monoamine neurotransmitter systems, which control feelings of sadness and loss of interest. The monoamine hypothesis indicates that deficiencies in serotonin, norepinephrine, and dopamine contribute to depressive symptoms. Recent studies have demonstrated that chronic stress can alter neuroplasticity in brain regions like the prefrontal cortex and hippocampus, potentially exacerbating depressive states (Fox and Lobo 2019). A review of biased cognition in depression discusses cognitive correlates of depressed mood and the neurochemical mechanisms underlying pessimistic judgment bias and abnormal response to negative feedback. Preclinical research has identified molecular and

neurophysiological mechanisms in reward circuitry that underlie behavioral constructs relevant to depressive symptoms (Milaneschi et al. 2020).

Preclinical research has identified molecular and neurophysiological mechanisms in reward circuitry that underlie behavioral constructs relevant to depressive symptoms. For instance, alterations in the mesolimbic dopamine pathway, which is crucial for reward processing, have been linked to anhedonia—a core symptom of depression characterized by a diminished ability to experience pleasure. This pathway's dysfunction is believed to be mediated by both genetic factors and environmental stressors, highlighting the complex interplay between nature and nurture in the development of depression.

Moreover, inflammation has emerged as a significant factor in the pathophysiology of depression. Elevated levels of pro-inflammatory cytokines have been observed in depressed individuals, suggesting that inflammation may contribute to the onset and maintenance of depressive symptoms. These cytokines can affect brain function by altering neurotransmitter metabolism, reducing the availability of serotonin and other key neurotransmitters, and influencing brain plasticity. Understanding the neurochemical underpinnings of depression has important implications for treatment. Traditional antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), aim to correct neurotransmitter imbalances by increasing the availability of serotonin in the brain. However, not all patients respond to these treatments, indicating the need for novel therapeutic approaches that target other aspects of depression's neurochemical and neurobiological basis. For example, anti-inflammatory agents and drugs that enhance neuroplasticity are currently being explored as potential treatments for depression.

2.3.2 Anxiety Disorders: Neuropharmacological Insights

Anxiety disorders, including GAD, panic disorder, OCD, and PTSD, are characterized by excessive and debilitating worry or fear (Leicht and Mulert 2020). Neurotransmitter dysregulation, especially involving serotonin, GABA, norepinephrine, and glutamate, plays a significant role in their pathophysiology (Chen 2016). The amygdala's fear response and emotional regulation disruptions mediated by the prefrontal cortex have been linked to specific changes in these systems (Hamilton et al. 2015). Neuroimaging studies have also contributed to our understanding of the structural and functional neuroanatomy of anxiety disorders, with the amygdala, insula, and anterior cingulate cortex being key regions involved in fear and anxiety (Melaragno et al. 2020). To treat these disorders, medications targeting these neurotransmitters have been developed, with SSRIs and SNRIs being the most common and effective ones due to their broad efficacy and tolerability (Nasir et al. 2020). However, alternative treatments are being explored as not all patients respond well to these medications. The glutamate system has emerged as a potential target for new anxiety disorder treatments, and medications that modulate glutamate neurotransmission are being investigated (Farach et al. 2012).

These neurotransmitter systems is complex, and disruptions in one system can influence others, contributing to the multifaceted nature of anxiety disorders. For instance, serotonin and GABA interactions are crucial for regulating the balance between excitatory and inhibitory signals in the brain, impacting overall emotional stability and response to stress. Neuroimaging studies have shed light on the neural correlates of anxiety disorders, revealing abnormalities in brain regions involved in emotional processing and regulation. The amygdala, a key structure in the fear circuit, shows hyperactivity in anxiety disorders, while the prefrontal cortex, which modulates emotional responses, often exhibits hypoactivity. The insula and anterior cingulate cortex are also implicated in the heightened sensitivity to anxiety-provoking stimuli and altered interoceptive awareness seen in these conditions.

2.3.3 Schizophrenia and Neurotransmitter Dysfunction

Schizophrenia is a chronic mental disorder that impacts a person's cognitive abilities, thinking, and perception. The cause of this disorder is attributed to complex issues with neurotransmitter function in the brain (Mısır and Akay 2023). According to the dopamine hypothesis, an overactive dopamine receptor in the brain's mesolimbic pathway contributes to positive symptoms, such as hallucinations and delusions. Meanwhile, cognitive impairments associated with schizophrenia are linked to disturbances in glutamate neurotransmission, particularly the NMDA receptors (Luvsannyam et al. 2022). The disease leads to a decline in information processing by affecting the synaptic connections in neural circuits (Heinz et al. 2019). Although the exact neurotransmitter changes in schizophrenia are not fully understood, subcortical dopamine dysfunction is considered a significant mechanism. Glutamate and GABA are also key neurotransmitters implicated in the disease, primarily in the neurocircuits that control cognitive and motivational aspects of behavior (Abboud et al. 2017). The dysfunction of the glutamatergic neurotransmitter system, specifically *N*-methyl-D-aspartate receptor hypofunction, is a significant factor in schizophrenia. Furthermore, abnormalities in the motor system have been identified as central to schizophrenia, with regions such as the basal ganglia and prefrontal cortex involved.

The dysfunction of neurotransmitters, particularly dopamine and glutamate, plays a crucial role in the development of schizophrenia (Abi-Dargham 2014) GABA, the primary inhibitory neurotransmitter, also plays a critical role in maintaining the balance of excitatory and inhibitory signals in the brain. Reduced GABAergic function in schizophrenia is thought to contribute to the hyperactivity of dopaminergic and glutamatergic systems, exacerbating symptoms. Pharmacological treatments for schizophrenia often target these neurotransmitter systems to alleviate symptoms. Antipsychotic medications, which primarily block dopamine D2 receptors, are effective in reducing positive symptoms but are less effective for negative symptoms and cognitive deficits. Research into new treatments is exploring the modulation of glutamatergic and GABAergic systems to

address these unmet needs. For example, NMDA receptor modulators and GABA agonists are being investigated for their potential to improve cognitive function and reduce negative symptoms.

2.3.4 Bipolar Disorder: Biochemical Perspectives

Bipolar disorder is a serious mood disorder that is thought to be caused by a combination of genetic and environmental factors (Young and Juruena 2020). The condition is characterized by a disruption in intracellular biochemical cascades, oxidative stress, and mitochondrial dysfunction, which can lead to a loss of neuronal plasticity and brain tissue (Machado-Vieira et al. 2004). Although animal models are limited in their ability to replicate the cyclical mood changes seen in humans, molecular genetic studies suggest that bipolar disorder is a complex condition that is inherited in a multifactorial pattern, with no single gene having a large effect (Angst 2008). Brain imaging studies have shown that individuals with bipolar disorder have abnormalities in the connectivity between the fronto-limbic circuits, but further research is needed to understand how these brain features contribute to the development and progression of the illness. Additionally, researchers have been working to distinguish bipolar disorder from unipolar depression and healthy subjects by studying brain function (Kato 2019). Bipolar disorder is characterized by alternating periods of mania and depression, which are believed to be caused by dysregulation in serotonin, dopamine, and norepinephrine systems, as well as disruptions in the hypothalamic-pituitary-adrenal (HPA) axis and circadian rhythms. Although the precise mechanisms underlying bipolar disorder are still unclear, these biological factors are believed to play a significant role in the development and progression of the condition (Gyulai and Young 2008).

The norepinephrine system is involved in the body's stress response and can influence mood, arousal, and alertness. Dysregulation in norepinephrine signaling can contribute to both manic and depressive symptoms. Additionally, disruptions in the HPA axis, which regulates the body's response to stress, have been observed in individuals with bipolar disorder. Abnormal cortisol levels, a key hormone in the HPA axis, are associated with mood episodes and can affect brain function and structure. Circadian rhythm disturbances are also a hallmark of bipolar disorder. The body's internal clock, which regulates sleep-wake cycles and other physiological processes, is often disrupted in individuals with bipolar disorder. These disruptions can lead to sleep disturbances, which are common in both manic and depressive episodes, and can exacerbate mood instability. Oxidative stress and mitochondrial dysfunction are emerging as important factors in the pathophysiology of bipolar disorder. Oxidative stress results from an imbalance between the production of reactive oxygen species (ROS) and the body's ability to detoxify these harmful compounds. Elevated levels of ROS can damage cellular components, including lipids, proteins, and DNA, leading to cellular dysfunction and death. Mitochondrial dysfunction, which impairs energy production in cells, can further contribute to

neuronal damage and loss of plasticity, which are observed in individuals with bipolar disorder. Understanding the biochemical underpinnings of bipolar disorder has important implications for treatment. Traditional mood stabilizers, such as lithium and valproate, are thought to exert their effects by modulating neurotransmitter systems and reducing oxidative stress. Antipsychotic medications, which are often used to treat manic episodes, target dopaminergic and serotonergic receptors to stabilize mood. Additionally, emerging treatments that target mitochondrial function and oxidative stress are being investigated for their potential to improve outcomes in bipolar disorder.

2.4 Neuropharmacological Treatments

Neuropharmacological treatments encompass a diverse range of medications that are specifically designed to target various nervous system conditions. These treatments work by focusing on specific neurotransmitters or neural pathways to ease symptoms and manage different disorders (Moisset et al. 2020). For instance, selective serotonin reuptake inhibitors (SSRIs) like Prozac and serotonin-norepinephrine reuptake inhibitors (SNRIs) like Effexor are commonly used to treat depression and certain anxiety disorders. Similarly, antipsychotics like Risperdal are used to manage conditions such as schizophrenia and bipolar disorder by regulating dopamine and serotonin levels in the brain. Anxiolytics such as benzodiazepines and buspirone act on gamma-aminobutyric acid (GABA) receptors to alleviate anxiety symptoms (Attal 2019).

It is essential to recognize that the wide range of medication categories available highlights the importance of tailored prescriptions and close monitoring by healthcare professionals to optimize efficacy and safety for individual patients. Neuropathic pain treatments also follow a personalized approach, starting with first-line options like tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, pregabalin, and gabapentin, and progressing to lidocaine plasters, capsaicin patches, tramadol as second-line treatments, and strong opioids and botulinum toxin A as third-line options (Johnson 2008).

Recent research has been exploring new pathways and therapies, potentially offering more options for managing these conditions. For example, there has been growing interest in the use of ketamine for treatment-resistant depression and other mood disorders. Ketamine works by regulating glutamate, which is a major excitatory neurotransmitter in the brain. Additionally, the use of transcranial magnetic stimulation (TMS) as a non-invasive treatment for depression has been gaining popularity (Johnson and Ait-Daoud 2000). It is evident that a multidimensional approach involving medications, psychotherapies, and personalized strategies is crucial for effectively managing these challenging conditions. This underscores the need for continual advancements and understanding in the field. Only by working collaboratively can healthcare professionals ensure that patients receive the best possible care and support (Attal 2011).

2.4.1 Psychotropic Medications and Their Modes of Action

Psychotropic medications refer to drugs that are utilized for treating various mental disorders. These medications have different modes of action that affect the brain and neurotransmitters in specific ways. One proposed method for categorizing psychotropic drugs suggests organizing them based on their pharmacologic mode of action, rather than their target disorder. Categorizing them according to their mode of action can provide a more logical and coherent nomenclature for these medications, as classifying them based on their target disorders can be perplexing due to their multiple therapeutic actions (Moisset et al. 2020). Additionally, psychotropic medications can serve as socializing agents, influencing an individual's sense of self and psychological development. The goal of using psychiatric medications is to assist adolescents in becoming responsible and emotionally intelligent individuals by teaching them how to manage their medications. Psychotropic medications have both indirect and direct biological effects, structuring adolescents' selves and social worlds through these pathways to the brain. While existing models of psychotropic drug action include the disease-centered and drug-centered models, they have their limitations. Alternatively, the patient-centered model of psychotropic drug action considers patient-related factors in determining drug effects. This model provides a comprehensive framework for understanding the actions of psychotropic drugs and can improve clinical practice and research. A new approach for classifying the therapeutic uses of psychotropic drugs is proposed, based on the interaction between their psychoactive effects and mental illness symptoms. Psychotropic drugs can be categorized on a continuum between psycho-antagonistic and psycho-agonistic modes, depending on their therapeutic uses and clinical responses. Psychotropic drugs target specific molecular sites involved in neurotransmission, such as transporters, G protein-coupled receptors, and enzymes (Moisset et al. 2020).

Psychotropic medications refer to a diverse range of drugs that are designed to modulate brain chemistry and address mental health conditions. Antidepressants, which include SSRIs, TCAs, and MAOIs, primarily affect neurotransmitter levels, particularly serotonin, by inhibiting its reuptake or altering its availability in the brain. Antipsychotics, categorized as typical and atypical, work by antagonizing dopamine receptors, especially the D2 subtype, to alleviate symptoms of psychosis. Atypical antipsychotics also target serotonin receptors. Anxiolytics like benzodiazepines augment the effects of GABA, an inhibitory neurotransmitter, inducing a calming effect (Rajkumar 2015). On the other hand, buspirone acts on serotonin receptors to mitigate anxiety. Mood stabilizers such as lithium modulate various neurotransmitter systems, regulating receptor sensitivity and neurotransmitter metabolism to stabilize mood in conditions such as bipolar disorder. Stimulants used in ADHD like methylphenidate and amphetamines heighten dopamine and norepinephrine levels, enhancing focus and attention. Anticonvulsants such as valproate and lamotrigine modify neurotransmitter activity, mainly affecting GABA and glutamate, to curb abnormal brain electrical activity seen in seizures and sometimes used as mood stabilizers. The modes of action of these medications highlight

their specific targeting of neurotransmitters, receptors, or neural pathways crucial in managing mental health disorders. Therefore, tailored prescriptions and careful monitoring are essential to optimize their effectiveness while minimizing potential side effects for everyone (Stahl 2013).

Psychotropic medications target specific molecular sites that have significant effects on neurotransmission, including transporters for neurotransmitters, receptors coupled to G proteins, and enzymes. There are two approaches to explaining the mechanism of action of psychotropic drugs: the disease-centered view and the drug-centered view. A new paradigm proposes classifying the therapeutic uses of psychotropic drugs based on their psychoactive effects and symptoms of mental illness, placing them on a continuum between psycho-antagonistic and psycho-agonistic modes. However, existing models of psychotropic drug action have limitations, and an integrative, patient-oriented model is proposed. This model acknowledges the importance of patient-related factors in determining drug effects and provides a unified framework for understanding the actions of psychotropic drugs. It is worth noting that psychiatric medications not only exert direct biological effects but also function as socializing agents, shaping sense of self and psychological development through moral discourse and social positioning (Rajkumar 2015).

2.4.2 Pharmacological Interventions for Various Disorders

Pharmacological interventions encompass a diverse array of treatments that aim to address physiological and neurological disorders. In the realm of psychiatry, antidepressants, specifically selective serotonin reuptake inhibitors (SSRIs) like Prozac and Zoloft, are a cornerstone in managing depression and certain anxiety disorders by increasing serotonin availability to regulate mood. Antipsychotics, both typical (such as haloperidol) and atypical (like risperidone), target dopamine receptors to alleviate symptoms of schizophrenia and bipolar disorder (Barra et al. 2022). Anxiolytics, including benzodiazepines (like Xanax) and buspirone, modulate GABA or serotonin receptors to reduce anxiety symptoms. In bipolar disorder management, mood stabilizers like lithium or anticonvulsants such as valproate stabilize mood swings and regulate neural excitability (Theleritis et al. 2023). Stimulants like Adderall and Ritalin increase dopamine and norepinephrine levels to improve focus and attention in ADHD treatment. Pain management incorporates opioids like morphine, nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, or anticonvulsants like gabapentin, each targeting different pain pathways. For epilepsy, anti-seizure medications like levetiracetam and phenytoin mitigate abnormal electrical activity. These pharmacological interventions use a variety of mechanisms, from neurotransmitter modulation to neural pathway alteration, to manage a wide range of disorders, each with its unique physiological and neurological underpinnings. Tailored prescriptions and close monitoring are crucial to optimize efficacy while minimizing potential side effects for individual patients (Peadon et al. 2017).

Pharmacological interventions play a significant role in the treatment and understanding of different mental disorders. These interventions not only provide potential treatments for mental disorders but also help uncover the neurobiological causes of these disorders. For instance, in the case of schizophrenia, antipsychotic drugs have been instrumental in revealing the role of abnormalities in the dopamine system. Similarly, interventions with antidepressant drugs have provided valuable insights into the neurobiological basis of depression. In addressing antagonistic traits such as aggression and interpersonal dysfunction in personality disorders, pharmacotherapy has been explored as a viable option. Medications like clozapine and second-generation antipsychotics have shown efficacy in reducing symptoms of severe personality disorders (Salvatore et al. 2016). In the management of apathy in patients with Alzheimer's Disease, pharmacological treatments such as donepezil, galantamine, and methylphenidate have been proven effective. Although the use of pharmacological interventions for individuals with autism spectrum disorder is still being investigated, certain medications have shown promise in addressing associated psychiatric disorders. Additionally, pharmacologic stimulants like amantadine, methylphenidate, and bromocriptine can support rehabilitation efforts in patients with disorders of consciousness (Usmani et al. 2011).

2.5 Role of Nutrition in Modulating Neurochemistry

Nutrition plays a crucial role in modulating neurochemistry, influencing the biochemical processes and neurotransmitter activity in the brain. A healthy diet, characterized by a higher intake of fruits, vegetables, whole grains, and good quality sources of protein, has been associated with a decreased risk of mood disorders, such as anxiety and depression. Specific nutrients and food compounds, such as dietary flavanols, omega-3 fatty acids, probiotics, and antioxidants, have been found to have beneficial effects on neurochemistry. Modulating the gut-brain axis through nutritional interventions, such as the modulation of gut microbiota, shows promise in the management of mood disorders. However, further research is needed to determine the optimal combination of nutrients and dosages for maximum benefit in modulating neurochemistry and managing mood disorders. Dietary fluctuations in nutrient availability can impact brain biochemistry and function, even within the range of maintaining normal nutritional status. Specific nutrients, such as vitamins, minerals, fatty acids, and trace elements, are essential for brain health and cognitive function. Nutritional deficiencies or imbalances can lead to neurological manifestations and exacerbate preexisting conditions. On the other hand, certain neurological diseases can also affect nutrition and the nutritional state of individuals. Recent research has shown that nutrition can influence the synthesis of neurotransmitters and the regulation of brain functions. Understanding the critical role of nutrition in brain health can help optimize brain function, prevent dysfunction, and treat diseases. For instance, omega-3 fatty acids found in fish oil can enhance cognitive function and reduce symptoms of depression, while antioxidants from fruits and

vegetables can protect neurons from oxidative stress. Additionally, the intake of probiotics can support gut health, which in turn influences brain function and mood through the gut-brain axis. Therefore, a comprehensive approach to diet and nutrition can significantly contribute to mental health and well-being, making it a valuable component of treatment strategies for psychiatric disorders.

2.5.1 Impact of Diet on Neurotransmitter Balance

The food we eat has a direct impact on the balance of neurotransmitters in our brain. Neurotransmitters are chemical messengers that carry information between nerve cells and play a crucial role in regulating mood, behavior, and cognitive function. The levels and activity of neurotransmitters can be influenced by the nutrients in our diet, such as amino acids, fatty acids, and carbohydrates. For example, the amino acid tryptophan, found in protein-rich foods, is a precursor for serotonin production, a neurotransmitter that affects mood and sleep. Consuming high-protein foods can decrease levels of tryptophan and serotonin in the brain, while carbohydrate-rich foods can have the opposite effect. Deficiencies or imbalances in nutrients can lead to dysfunction in neurotransmitter synthesis and transmission, which can impact mood, behavior, and cognitive function. On the other hand, a balanced and nutrient-rich diet, such as the Mediterranean diet, has been shown to have a positive impact on brain function and reduce the risk of neurodegenerative diseases (Smith and Scholey 2014).

The balance of neurotransmitters in the brain is influenced by diet. Certain nutrients, such as amino acids, glucose, vitamins, and minerals, play a role in the production and release of neurotransmitters. Polyunsaturated fatty acids, like omega-3 fatty acids, are important for the function of the nervous system. Additionally, the presence of antioxidants in the diet can protect against oxidative damage to brain cells (Mattei and Pietrobelli 2019). The food we consume can also affect the permeability of cell membranes and neurotransmitter metabolism. Furthermore, specific dietary patterns, such as the Mediterranean diet, have been shown to have a positive impact on brain function and a lower incidence of neurodegenerative diseases (Smith and Scholey 2014).

Overall, the impact of diet on neurotransmitter balance highlights the importance of proper nutrition for maintaining optimal brain function and mental well-being. Nutrition plays a crucial role in maintaining the balance of neurotransmitters in the brain, which in turn affects cognitive function and behavior (Dauncey 2009). A well-balanced diet that includes a variety of nutrients can support neurotransmitter synthesis and function, promoting mental health and reducing the risk of psychiatric and neurodegenerative disorders.

2.5.2 Nutritional Strategies for Managing Psychiatric Conditions

Nutritional strategies for managing psychiatric conditions involve the use of specific nutrients and dietary patterns. Studies have shown that supplementation with nutrients such as omega-3 fats, vitamin D, probiotics, methyl folate, and S-adenosyl methionine can be helpful for conditions like depression. A healthy diet, characterized by high intake of fruits, vegetables, whole grains, and good quality sources of protein, has been associated with decreased risk of mood disorders. On the other hand, diets high in saturated fats, refined sugars, caffeine, alcohol, and processed foods have been linked to poor prognosis. The bidirectional interaction between the brain and the gut, known as the gut-brain axis, plays a key role in the link between nutrition and mood disorders. However, the efficacy of nutraceuticals in psychiatric disorders is still uncertain, and more personalized approaches are needed, considering biomarkers, dietary patterns, and individual nutrient requirements. Overall, there is a need for further research to determine the specific nutrients and doses that are most effective in managing psychiatric conditions.

Nutritional strategies play a significant role in managing psychiatric conditions. Observational studies have shown that a healthy diet, characterized by a higher intake of fruits, vegetables, whole grains, and good-quality sources of protein, is associated with a decreased risk of mood disorders. Specific nutrients and food compounds, such as omega-3 fatty acids, minerals like magnesium and zinc, B vitamins, and antioxidants found in fruits and vegetables, have been linked to improved outcomes in the management of conditions like bipolar disorder and post-traumatic stress disorder. Additionally, the modulation of the gut-brain axis through nutrition-based strategies, such as the use of probiotics and the avoidance of diets high in saturated fats and refined sugars, shows promise in the prevention and treatment of psychiatric illnesses. However, further research is needed to refine and scale up dietary interventions for maximum benefit in managing these conditions and to determine the optimal nutritional approaches for individual patients.

Specific nutritional interventions have shown promise in managing psychiatric conditions. Omega-3 fatty acids, found in fish oil and certain plant oils, have anti-inflammatory properties and can modulate neurotransmitter pathways, which are beneficial in conditions like depression and bipolar disorder. Vitamin D, often referred to as the "sunshine vitamin," is important for brain health, and low levels have been linked to an increased risk of depression. Probiotics, which maintain gut health and are linked to mental health through the gutbrain axis, can help manage symptoms of depression and anxiety. Methyl folate, a form of folate readily used by the body, plays a role in neurotransmitter synthesis and has been found effective in managing depression. S-adenosyl methionine (SAMe), involved in neurotransmitter synthesis, has shown promise in treating depression. Minerals like magnesium and zinc, essential for brain health, are often deficient in individuals with depression and anxiety, and their supplementation can improve mood and cognitive function. Dietary patterns also play a crucial role in mental health. The Mediterranean diet,

rich in fruits, vegetables, whole grains, fish, and olive oil, is associated with a reduced risk of depression and cognitive decline. An anti-inflammatory diet, emphasizing foods that reduce inflammation such as fruits, vegetables, nuts, and fatty fish, can help manage psychiatric conditions linked to neuroinflammation. Avoiding processed foods, refined sugars, and unhealthy fats is crucial, as these are associated with a higher risk of psychiatric disorders. Reducing intake of these foods can improve mental health outcomes. Personalized nutrition takes into account individual differences in genetics, metabolism, and lifestyle to create tailored dietary plans. Biomarkers and genetic testing can help identify specific nutrient needs and potential deficiencies, allowing for more effective and individualized nutritional interventions.

2.6 Conclusion

The relationship between neuropharmacology and nutritional interventions underscores the profound impact of dietary components on neurological function and mental health. Neurotransmitters play a critical role in the regulation of mood, cognition, and behavior, and their dysregulation is linked to various psychiatric disorders such as depression, anxiety, schizophrenia, and bipolar disorder. Neuropharmacological treatments, which target specific neurotransmitter systems, have been pivotal in managing these conditions, providing relief from symptoms, and improving patients' quality of life. However, pharmacological interventions alone may not be sufficient. The field of nutritional psychiatry highlights the importance of integrating dietary strategies to enhance neurochemical balance and support mental health. Specific nutrients, such as omega-3 fatty acids, vitamins, and probiotics, have been shown to influence neurotransmitter synthesis, receptor activity, and neuronal plasticity. These findings suggest that a combined approach, incorporating both pharmacological and nutritional interventions, can lead to more effective and holistic management of psychiatric disorders. Further research is essential to unravel the complex mechanisms underlying the interaction between diet and brain function. Such investigations could pave the way for new therapeutic options, including personalized nutritional plans tailored to individual neurochemical profiles. By adopting an interdisciplinary perspective that integrates neuropharmacology and nutritional science, healthcare professionals can develop innovative, patient-centric treatments that address the multifaceted nature of psychiatric disorders. This approach promises to redefine the management of mental health conditions, ultimately enhancing patient outcomes and well-being.

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Chapter 3
Human Nutritional Neuroscience: Fundamental Issues

Walaa H. Foula and Waleed M. Foad

Abstract Human Nutritional Neuroscience, an interdisciplinary field, delves into the intricate relationship between diet and brain health, exploring the impact of various dietary components on brain structure, function, and behavior.

This chapter goes through the multifaceted relationship between diet and brain health within the realm of Human Nutritional Neuroscience. Beginning with an exploration of the metabolic impact of diet on brain health, the narrative progresses to illuminate the importance of nutrition in the development of brain. Investigating the intricate interplay of various food constituents on human behavior, the discussion unfolds to scrutinize the distinct influences of macronutrients and micronutrients on brain function. A spotlight is cast on the emerging understanding of gut-brain axis and its profound implications for mental well-being.

The complex connection between cognition and feeding is dissected, shedding light on the bidirectional relationship between what we eat and our cognitive processes. Methodologies for assessing nutritional effects on brain function and behavior in humans are scrutinized, emphasizing the need for rigorous scientific examination. The burgeoning field of Nutritional Psychiatry is explored, providing insights into how dietary choices may influence mental health.

Keywords Nutritional neuroscience · Brain health · Gut-brain axis · Nutritional psychiatry

3.1 Introduction

Human Nutritional Neuroscience is an interdisciplinary scientific field that concentrates on the effect of diet and nutrition on brain structure, function, and behavior. It examines how different aspects of one's diet, including minerals, vitamins, proteins, carbohydrates, lipids, supplements for diet, synthetic hormones, and food additives

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affect neurobiology, neurochemistry, conduct, and cognitive abilities. This emerging discipline seeks to understand how the chemicals found in foods we ingest can influence brain functions like memory, mood, learning, and behavior. This field has gained increased attention in recent years as it is recognized that diet and nutrition can have profound effects on brain health, cognitive function, and mental well-being, and that micronutrients from nutrition may prevent or treat neurological and psychological conditions.

Recent studies exploring the nutritional processes and their impact on the brain have evidenced that they have a role in nearly every aspect of neurological performance, malnutrition involves changes in neurogenesis, neurotrophic factors, neural networks, and neuroplasticity through lifespan (Dauncey 2009).

This research highlights how the foods and molecules we consume can influence the structure and function of the brain from development through adulthood and aging by influencing neuronal growth, maintenance, and connectivity inside the central nervous system (Dauncey 2009).

Examination of the relation between nutrition and human behavior faces challenges. Assessing human behavior is inherently limited, and there are numerous contentious issues in the area of human behavior analysis. Also, our understanding of the crucial nutritional factors influencing human behavior is insufficient, particularly concerning the potential effects of persistent dietary changes. Nevertheless, there is a widespread interest in immediate and prolonged impacts of diet on society behavior.

Various dietary supplements claiming to improve cognitive performance or facilitate loss of weight by modifying behavior are heavily promoted. Products asserting benefits for stress relief, depression alleviation, or memory enhancement are also prevalent. Additionally, numerous foods and supplements claiming to boost energy levels are readily accessible. However, the scientific evidence supporting that claims is frequently not strong or unavailable.

Therefore, the primary goal in the field of nutrition and behavior should be to develop reliable ways to substantiate or refute the claims of manufacturers, sellers, and the media. It is critical that scientists reach consensus on appropriate methods and interpret data to gain a unified understanding of key issues. This consensus will enable evidence-based policy recommendations to be made to government agencies and consumers when commercial organizations make behavioral claims about their products.

When business entities assert the behavioral benefits of their products, such as the ability to improve specific elements of cognitive performance and mood, including memory, stress relief, mental energy, depression, and anxiety, it is imperative that the underlying evidence is behavioral in nature. Although secondary endpoints, such as physiological or biochemical markers, are of great scientific importance, they cannot be considered suitable alternatives to functional outcomes when claims relate to changes in human behavior.

3.2 Metabolic Impact of Diet on Brain Health

While the brain only constitutes around 2% of total body mass, it accounts for 20–25% of the body's total energy usage (Fonseca-Azevedo and Herculano-Houzel 2012). Relatively speaking then, the brain demands an immense amount of fuel compared to other organs. For this reason, the processes involved in transforming nutrients from foods into usable energy for neurons are probably essential for governing brain functionality (Gómez-Pinilla 2008). Not getting enough of certain vitamins or suffering from particular metabolic conditions has been shown to impact cognitive abilities by interfering with the nutrient-dependent body systems responsible for managing neuronal energy levels (Gómez-Pinilla 2008). Disruptions to these energy management processes can then negatively influence aspects of brain activity like neurotransmission, synaptic plasticity, and neuron survival rates (Gómez-Pinilla 2008).

Processes related to energy management in neurons can affect synaptic plasticity (Vaynman et al. 2006), providing insight into how metabolic disorders affect cognitive processes. Interestingly, synaptic function can mutually affect metabolic energy, enabling mental processes to affect bodily function at the molecular level. Brain-derived neurotrophic factor (BDNF) serves as an excellent example of a signaling molecule closely related to both energy metabolism and synaptic plasticity. BDNF is most abundant in brain regions associated with cognitive regulation and metabolism—the hippocampus and hypothalamus, respectively (Nawa et al. 1995). BDNF influences various aspects of energy metabolism, including suppression of appetite (Kernie et al. 2000; Lyons 1999), insulin sensitivity (Pelleymounter et al. 1995; Nakagawa et al. 2002), and glucose (Tonra et al. 1999) and lipid metabolism (Tsuchida et al. 2002). The melanocortin receptor 4 of the hypothalamus, which is essential for controlling energy balance, regulates BDNF expression in the ventral medial hypothalamus (Xu et al. 2003), strengthening the relationship between energy metabolism and synaptic plasticity.

Studies in rodents suggest that the disruption of energy metabolism, such as by injecting high-dose vitamin D3 into the brain, may negate the effects of exercise on the final effects of BDNF-mediated synaptic plasticity (Vaynman et al. 2006). In humans, a de novo mutation in TrkB, a BDNF receptor, has been associated with hyperphagic obesity, as well as impaired learning and memory (Yeo et al. 2004). Further research is needed to determine the limits of the relationship between energy metabolism and synaptic plasticity mediated by BDNF to alter cognitive function.

Research has shown that dietary patterns can affect the health of brain significantly. For example, a Mediterranean diet, which is rich in whole grains, fruits, vegetables, and lean protein, has been related with lower risk of dementia and better cognitive function (Drouka et al. 2022). The term "Mediterranean diet" (MD) relates to the customary eating patterns of individuals residing in regions such as Crete, Italy, and other areas of Mediterranean. This diet is characterized by a rich inclusion of plant foods, including fruits, vegetables, legumes, nuts cereals, and seeds. Olive oil serves as the main source of fat. Additionally, the MD contains

moderate amounts of dairy products, especially yogurt and cheese, along with varying but generally low to moderate amounts of fish and poultry. Red meat is consumed in limited amounts, and wine is enjoyed in moderation.

In addition to dietary patterns, specific nutrients have been shown to have beneficial effects on the brain. For example, amid the combination of epidemiological and experimental evidence, various clinical studies underscore the potential benefits of omega 3-rich oils in conditions, encompassing but not restricted to, bipolar depression (Balanzá-Martínez et al. 2011), posttraumatic stress disorder (Matsuoka et al. 2010), major depression (Su et al. 2013), and the indicated prevention of psychosis (Amminger et al. 2010). Conversely, considering the brain's continual reliance on a diverse array of nutrients for its structure and function, coupled with the potential metabolic errors implicated in mental disorders, the conventional emphasis on resolving issues with a single nutrient (Rucklidge et al. 2013) may obscure the potential advantages of multi-nutrient interventions (Rucklidge and Kaplan 2013). Zinc serves as a pertinent example. The findings from numerous preclinical and clinical studies suggest that zinc supplementation could be beneficial for individuals dealing with major depression (Solati et al. 2015). In addition, dietary low zinc has not been shown to be associated with depression only (Swardfager et al. 2013) but has also been related to abnormal response to antidepressant drugs (Młyniec et al. 2013).

Similarly, B vitamins, particularly folate, have been shown to be important for brain health and may help decrease the risk of dementia (Wang et al. 2022).

3.3 Role of Nutrition in the Development of Brain

The progression of the brain's growth and development follows a diverse trajectory over time (Fox et al. 2010). A significant part of the final structure of the brain and its capabilities are formed during the first years, particularly before the age of three. Recognizing and delineating this notably sensitive period has refined the strategies employed by public policies aimed at fostering healthy brain development. The implications of this understanding are significant, as failure to improve brain development in the early stages appears to produce lasting effects on aspects such as education, employment prospects, and the mental well-being of adults (Walker et al. 2007). These enduring consequences represent the "ultimate cost to society" resulting from adversity experienced early in life.

The brain is characterized by its heterogenous structure, consisting of various anatomical regions and processes, such as myelination, each following distinct developmental paths (Fox et al. 2010). Many of these regions initiate and undergo rapid development during fetus life or after birth within short time. For instance, myelination experiences a sudden surge at 32 weeks of fetal life and is very active in the first 2 years postnatal (Fox et al. 2010). The monoamine neurotransmitter systems responsible for regulating reward, mood, and affect commence their development before birth (Field et al. 2008), progressing rapidly until at least the age of

3 years. The hippocampus, essential for functions like recognition and spatial memory, enters a phase of rapid growth around 32 weeks gestation, extending through the first 18 months postnatal (Fox et al. 2010; Rice and Barone Jr 2000). Even prefrontal cortex, which is responsible for coordinating more complex processing behaviors such as multitasking and attention, begins the period of accelerated growth during the first 6 months after birth (Fox et al. 2010; Rice and Barone Jr 2000). Ensuring that different brain areas stay on their respective developmental trajectories is crucial not just for promoting behaviors specific to individual regions but, more significantly, to facilitate the simultaneous development of brain regions designed to work together as circuits that support complex behaviors (White and McDonald 2002).

Early life occurrences, encompassing factors like nutritional insufficiencies and toxic stress, could yield distinct impacts on the development of brain areas and its processes, depends on the amount, time, and duration of these events (Kretchmer et al. 1996). Emphasizing the significance of timing is crucial (Cusick and Georgieff 2012), especially considering the disparate timing of peak developmental rates in the hippocampus and prefrontal cortex. The specific timing of an adverse environmental incident, affecting the dendritic arborization of neurons, for example, determines whether the hippocampus or prefrontal cortex carries a greater burden and tests a compromise in functional integrity.

The susceptibility of the brain's developed process, area, or circuit to early undernutrition depends on two factors: the timing of undernutrition and the region's need for that nutrient during that specific time period (Cusick and Georgieff 2016). For instance, protein, carbohydrates, LC-PUFA, iron, zinc, copper, iodine, vitamin A, vitamin B6, vitamin C, and vitamin D are some of the nutrients that affect the anatomy of neurons, oligodendrocytes, and other cell types. Similarly, nutrients like carbohydrates, protein, iron, selenium, iodine, zinc, vitamin B6, and B12 affect myelination, while protein, vitamin D, iron, copper, zinc, selenium, choline, and iodine affect the chemistry of neurons and astrocytes. Lastly, protein, glucose, iron, iodine, zinc, copper, and choline affect the physiology and metabolism of neurons and oligodendrocytes (Cusick and Georgieff 2016).

3.4 Food Constituents Affecting Human Behavior

Human studies examining the behavioral effects of nutrients, nutritional components, and supplements have concentrated on four categories of substances: first: macronutrients; carbohydrates, proteins, and fats, second: micronutrients; vitamins, and minerals, third: dietary constituents, for example, caffeine, and fourth: dietary supplements such as St. John's Wort, Ginkgo biloba, and melatonin. The fundamental principles in this field of nutritional neuroscience derive from related areas like experimental and psychopharmacology psychology.

It is well recognized that food ingredients tend to produce less dramatic effects on behavior compared to medications that affect same systems (Lieberman et al.

1982, 1986; Wurtman 1982). This relative lack of potency is not surprising since natural products with strong brain impacts are often categorized as medicines, addictive substances, or poisons. Examples include tetrodotoxin from fugu fish, scopolamine from nightshade, and opium from poppy.

The hidden effects of nutritional components on the brain and behavior impede the work of scientists in this area. As a result of the modest sizes of nutritional factors' behavioral changes, there is more disagreement on core issues than in allied fields like psychopharmacology where consensus is readily reached. Thus, rigorously designed behavioral methods are particularly critical here so researchers can reliably replicate each other's results and develop agreement on key topics.

Among individual food ingredients, caffeine appears to be the clearest example of one affecting human behavior based on literature overviews, with stimulant properties (Lieberman et al. 1987). While many other nutrients and supplements also seem to impact behavior as discussed in this book, unequivocal scientific agreement does not exist for these in the way it does for caffeine. Therefore, with the exception of caffeine, we lack established consensus on generally recognized behavioral effects of dietary components.

3.5 Macronutrients and Brain Function

The great demand of the human brain for energy highlights the vital role of macronutrients—carbohydrates, protein, and fat—in supporting optimal brain function. From neurodevelopment to cognitive performance, the food significantly impacts the mental agility, memory, and overall well-being.

3.5.1 Glucose: The Brain's Preferred Fuel

Carbohydrates are the main source of readily available fuel of the brain. Glucose, derived from carbohydrate digestion, fuels both neuronal function and the synthesis of neurotransmitters, essential chemicals for communication between brain cells. Studies consistently demonstrate that sufficient carbohydrate intake is crucial for cognitive performance, particularly memory, learning, and attention. However, the type of carbohydrates consumed makes a crucial difference.

Research suggests that low Glycemic Index carbohydrates improved memory in humans rather than high Glycemic Index carbohydrates (Benton et al. 2003).

3.5.2 Protein: Building Blocks for Structure and Function

Protein plays an important role in building and maintaining complex brain structure and function. Amino acids, the building blocks of proteins, are essential for the formation of neurons, neurotransmitters, and myelin, the lipid sheath that isolates nerve fibers and facilitates the rapid transmission of signals. Proper intake of protein has been related to improvement in cognitive function, memory consolidation, and learning abilities.

A meta-analysis by Coelho-Junior et al. (2021) did not find significant associations between protein intake and overall cognitive function in older adults. The cross-sectional study of Li et al. (2020) found a positive association between protein intake from animal foods, and pulses and cognitive function.

3.5.3 Fat: The Essential Ingredient for Brain Development and Protection

Long-chain polyunsaturated fatty acids (LC-PUFAs), specifically Omega 3 fatty acids, specifically docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), not only influence neurotransmission but also contribute to the reduction of neuroinflammation while supporting neuronal survival and neurogenesis (Bazinet and Layé 2014). DHA's significance extends to essential roles in neurogenesis, synaptogenesis, neuronal migration, fatty acid composition of membrane, and fluidity, particularly impacting neurotransmitter systems such as those involved in the visual system. These brain regions are involved in the control of attention, inhibition, and impulsivity (Cusick and Georgieff 2016). PUFAs, through their anti-thrombotic and anti-inflammatory properties, contribute in sustaining cognitive abilities and dementia prevention, influencing various neural processes (Gillette-Guyonnet et al. 2013). A retrospective study conducted in China found that the decline in cognitive function in the elderly was associated with higher energy levels of protein and fat than carbohydrates (Ding et al. 2018). In addition, insufficient intake of omega-3 PUFAs can be related to loss of memory (Spencer et al. 2017).

Several studies involving adults and elderly have shown that a high-fat diet can have negative impact on cognition. A longitudinal study of 6183 old age females in the USA found that high levels of saturated fatty acids were associated with impaired cognitive and verbal memory pathways, while higher intake of monounsaturated fatty acids (MUFA) was associated with more appropriate pathways (Okereke et al. 2012). Francis and Stevenson's review highlighted an association between a high saturated fat diet rich in refined carbohydrates and impaired cognitive function (Francis and Stevenson 2013). Consuming a high-fat diet prompts the hippocampus to generate a neuro-inflammatory response, even in the face of a mild immune challenge, resulting in memory deficits (Spencer et al. 2017). A high-fat diet also increases the risk of obesity, increases the likelihood of diabetes, and contributes to

the emergence of cognitive deficits, which can lead to Alzheimer's disease (AD). Known risk factors for AD, such as impaired glucose tolerance, insulin resistance, and type 2 diabetes mellitus, are exacerbated by a high-fat diet (Barbagallo and Dominguez 2014). Although data on the effects of high dietary protein are inconclusive, it has been identified that diets low in fat seem protective against cognitive decline.

It should be noted that the synergistic effect of macronutrients exerts a supportive effect that goes beyond the individual role played by each. A balanced diet incorporating a variety of complex carbohydrates, lean protein sources, and healthy fats provides the brain with the full spectrum of nutrients it needs to thrive. This comprehensive approach ensures optimal energy production, neurotransmitter function, and protection from oxidative stress, ultimately promoting cognitive health and well-being.

3.6 Micronutrients and Brain Function

Micronutrients play an important role in the synthesis of important compounds necessary for proper growth and development including enzymes, hormones (World Health Organization 2021). Among the critical public health concerns globally, deficiencies in vitamin A, iodine, and iron have substantial effects on the health of populations, especially impacting children and childbearing women in poor countries (World Health Organization 2021). Although recent research has explored the importance of vitamin B complex in development of the brain, there has been limited evidence in the past decade regarding the connection between fat-soluble vitamins and early-life cognitive development. A lot of studies have predominantly concentrated on their role in cognitive deterioration during later stages of life.

Vitamin B complex plays a crucial role in brain function and its development through various mechanisms. Venkatramanan et al. (2016) underscored the significance of maintaining sufficient vitamin B12 levels, particularly during childbearing period and childhood, as vitamin B12 is involved in brain development, nerve myelination, and fetal and child growth.

The importance of vitamin D in cognition and brain health has become apparent, with studies suggesting lower serum levels of 25-hydroxyvitamin D (25(OH) D in individuals with impaired cognitive function and Alzheimer's disease (AD) compared to healthy controls (Goodwill and Szoeke 2017; Afzal et al. 2014). In addition, low levels of vitamin D were found to increase the risk of Alzheimer's disease after 7 years (Annweiler et al. 2012). A study was conducted over 18 weeks comparing high dose of vitamin D3 (4000 IU/day) to low dose supplementation (400 IU/day) in healthy people highlighting that with high-dose vitamin D, visuospatial memory only had been improved and not other cognitive domains (Pettersen 2017). Executive dysfunction was predicted by low serum concentrations 25(OH)D, according to a review by Annweiler et al. (2013), while the association with episodic memory remained inconclusive (Annweiler et al. 2013). Meta-analysis

observed cognitive impairment in patients with vitamin D deficiency (Etgen et al. 2012). A systematic review by van der Schaft et al. (2013) stated that poor results on various cognitive tests were associated with an increased risk of dementia in people with low levels 25 (OH) D. Vitamin D deficiency was also associated with a subjective complaint predicting cognitive decline and dementia (Landel et al. 2016).

As for antioxidant vitamins (E and C), while several studies indicate a lower risk of cognitive deterioration with their intake, different results have been reported. Taking vitamin E and C supplements reduces the risk of cognitive deterioration in a prospective Canadian cohort (Basambombo et al. 2017). However, studies have also reported no link (Nooyens et al. 2015) or reverse association (Galasko et al. 2012) between antioxidants and cognition. A cross-sectional study in the USA associated high intake of vitamin E with a higher score in immediate recall, verbal memory, and better language/verbal fluency performance (Beydoun et al. 2015). Another cross-sectional study by Chouet et al. (2015) on 192 French older adults reported that dietary elevated vitamin K was associated with better cognition-related behavior among older adults.

Iron is an essential component of hemoglobin, necessary for the transport of oxygen to all organs of the body, including the brain. Iron deficiency anemia (IDA) forms a risk of cognitive impairment on both short and long term. IDA is associated with impaired mental and motor development in childhood, suboptimal cognition, and school performance during later childhood (Prado and Dewey 2014). Preventing iron deficiency is better than curing it. It is possible to protect the brain from an under-iron state at an early age, such as during fetal life and early childhood (Cusick and Georgieff 2016). Iron deficiency in the brain is associated with disrupted neurophysiological mechanisms, compromising cognitive and motor development, including impaired coordination, attention, executive function, and memory (Smyth et al. 2015).

Conversely, brain overload of iron also disrupts neurophysiological mechanisms, leading to increased oxidative stress, neuron death, decreased motor and cognitive functions, such as slow motor function, altered feedback processing and sensitivity, memory loss, and poor decision-making (Ferreira et al. 2019).

3.7 The Gut-Brain Axis

Another fundamental problem in human nutritional neurology is the gut and brain axis. The intestines and brain are connected via a complex network of nerves, hormones, and signal molecules. Research has shown that the gut microbiome, a group of microorganisms that live in the gut, has an important role in this regard (Cryan and O'Mahony 2011).

People are colonized by the coexisting gut microbiota in the first days of life. Recent research highlights the importance of microbiota in maintaining normal and healthy brain function. This understanding extends to the complex relationship between stress and microbiota, showing how changes in microbiota composition

can influence stress-related behaviors (Foster and Neufeld 2013). Emerging studies suggest that several bacteria, which include symbiotic, probiotic, and pathogenic species in the gastrointestinal tract (GI), have the ability to activate neural pathways and signaling systems of the central nervous system (CNS).

Recent investigations and the future ones, involving clinical and animal trials, directed at uncovering the intricacies of the microbiota-gut-brain axis hold promise for providing novel ways to prevent and treat mental illnesses, including anxiety and depression. The evolving understanding of how the microbiota influences brain function opens avenues for novel therapeutic interventions and preventive strategies targeting the intricate interplay between gut microbes and mental health.

One approach employed in investigating the microbiome-gut-brain axis involves the use of germ-free animals (Gareau et al. 2011), such as germ-free mice. These animals which are free from any bacterial contamination provide an opportunity to examine how the total lack of gastrointestinal microflora influences behavior. Additionally, germ-free mice enable the study of the isolated impact of specific entities, such as probiotics, on the microbiome-gut-brain axis. While these germ-free animals serve as valuable approach in neuro-gastroenterology research, the results derived from such studies cannot be directly translated to human pathology. This limitation arises because these animal models do not accurately represent real-world situations in the human population.

In one study (Neufeld et al. 2011), the authors utilized female mice free of germs to illustrate that the lack of a normal microflora leads to a reduction in anxiety behavior, as shown in the raised plus maze: a well-validated model of anxiolytic action. The study revealed an increase in the expression of brain-derived neurotrophic factor BDNF mRNA in the hippocampal dentate gyrus in these animals. BDNF is important to support the survival of neurons, promote the development and differentiation of new neurons and synapses, and therefore participate in the regulation of various aspects of emotional and cognitive behavior (Zola et al. 2000).

These findings collectively offer crucial proof that the microflora can affect both human behaviors and brains, particularly in the context of anxiety. The study builds upon previous research by Sudo et al. (2004), indicating that male mice free of germs exhibit an exaggerated response to stress, in addition to decreased hippocampal and cortical BDNF, as well as decreased NR1 (hippocampus) and NR2A (hippocampus and cortex).

Gut microbiome and a range of brain conditions had been related together, including anxiety, depression, and autism spectrum disorder. Furthermore, certain dietary patterns can have influence on gut microbiome, which can affect brain function and behavior.

3.8 Cognition and Feeding

The influence of feeding on cognition is totally related to neural circuits responsible for feeding behavior, demonstrating accurate coordination with centers of the brain regulating energy balance and cognition (Gómez-Pinilla 2008). The effect of food on emotion and cognition begins even before the action of eating, since remembering food through olfactory and visual sensory input can alter the emotional state of the brain. When ingested, foods stimulate the secretion of hormones and peptides, such as insulin and glucagon-like peptide 1 (GLP1) (McNay 2007), which circulate and reach centers like the hypothalamus and hippocampus. This activation sets off signal-transduction pathways that enhance synaptic activity, contributing to memory and ability to learn.

Conversely, the absence of food, signaled by an empty stomach, prompts the release of ghrelin, which as well supports cognitive function and synaptic plasticity. Chemical messages from adipose tissue through leptin can activate specific receptors in the hippocampus and hypothalamus, influencing learning and memory. Leptin's positive effects on hippocampus-dependent synaptic plasticity, particularly its actions on NMDA (N-methyl-D-aspartate) receptor function and facilitation of long-term potentiation, are well-documented (Harvey 2007). Insulin-like growth factor 1 (IGF1), which is produced in response to metabolic signals and exercise, can send signals to neurons in the hypothalamus and hippocampus, affecting learning and memory performance.

Beyond appetite regulation, the hypothalamus coordinates gut activity and integrates visceral function with limbic-system structures such as the hippocampus, amygdala, and cerebral cortex. Visceral signals from the gut can also inflect cognition and body physiology through the hypothalamic-pituitary axis (HPA). The hypothalamus, which largely innervates the thymus, can interact with the immune system, and immune system molecules can influence cognition and synaptic plasticity. Parasympathetic innervation of the gut provided by the vagus nerve provides sensory information to the brain, allowing gut activity to influence emotions. Reciprocally, emotions can influence the viscera through parasympathetic influences on the vagus nerve, and therapeutic applications such as vagus nerve stimulation are used to treat chronic depression.

3.9 Nutrition and Mental Health

Finally, there are a lot of evidences that nutrition plays a crucial role in mental health. For instance, higher intakes of processed foods and sugars have been associated with increased risk of depression and anxiety, while diets rich in vegetables, fruits, and whole grains have been associated with lower risk.

In addition, certain nutrients have been shown to be beneficial for mental health. For example, low levels of omega-3 fatty acids can increase the risk of depression and other mental illnesses.

3.10 Assessing Nutritional Effects on Brain Function and Behavior in Humans

Assessing the nutritional effects on the brain is challenging due to the heterogeneity of human populations, the variability of dietary intake, the difficulty of measuring brain activity, and the confounding factors of genetics, environment, and lifestyle. Some of the most commonly used methods and tools to assess the nutritional effects on brain function and behavior in humans are neuroimaging, neuropsychological tests, biomarkers, and dietary assessment.

Various MRI techniques, coupled with postprocessing analysis, enable the comprehensive examination of different aspects of cerebral health, encompassing macrostructure, microstructure, metabolism, and function. These techniques offer valuable understandings of brain development and aging, as well as in intervention studies, including those related to nutrition.

1. Cerebral Macrostructure (3D-volumetry): Three-dimensional volumetric analysis through MRI allows the assessment of the overall macrostructure of the brain. This involves measuring and analyzing the volume of different brain regions, providing insights into structural changes and variations over time.
2. Microstructure (Diffusion MRI): Diffusion MRI is a powerful tool for investigating microstructural features of the brain. It measures the diffusion of water molecules in tissues, offering information about the integrity of white matter tracts, cellular organization, and structural connectivity.
3. Metabolism (Magnetic Resonance Spectroscopy—MRS): MRS is used to assess the metabolic profile of the brain. It provides information about the concentrations of various metabolites, such as neurotransmitters and markers of cellular health, offering insights into the metabolic processes occurring within the brain.
4. Function (Functional MRI—fMRI): fMRI captures the dynamic functional activity of the brain by measuring changes in blood flow. This technique is widely used to study brain activation patterns associated with different tasks or stimuli, providing information about brain function and connectivity.

The application of these MRI techniques, along with advanced postprocessing analyses, not only facilitates the understanding of the normal development and aging of the brain but also allows researchers to investigate the impact of interventions, including nutritional interventions. This multidimensional approach contributes to a comprehensive understanding of brain health and aids in the design and evaluation of strategies to promote and maintain cognitive well-being.

While preclinical studies play a crucial role in elucidating underlying mechanisms, their reliance on non-physiological interventions, such as germ-free animals, simplified models of complex human emotions like anxiety and depression, and assumptions about the anatomical and functional homology between rodent and human brains, particularly in the prefrontal cortex and anterior insula, raise questions about their translational relevance to understand brain or brain-gut disorders in humans (Mayer et al. 2014). As a result, the true applicability of findings from these rodent models in a human context remains unclear. To ascertain the validity of intriguing animal findings, more research involving human subjects is imperative.

Functional magnetic resonance imaging (fMRI) in humans offers a means to detect changes in brain response following interventions like probiotics or antibiotics, similar to its conventional use in testing behavioral or pharmaceutical interventions (Mayer et al. 2002; Wise and Tracey 2006; Tillisch et al. 2008). A study on healthy women without gastrointestinal symptoms, pain, or psychiatric disorders investigated the impact of consumption of probiotic every day on brain responses to an emotion recognition task (Tillisch et al. 2013). In this randomized trial, women received a probiotic, a nonfermented dairy product, or no treatment. The fMRI results before and after the treatment period revealed that the probiotic group showed reduced responses in the insula and somatosensory cortex, as well as across a widespread functional network that includes emotional and sensory regions compared to both control groups. Although there are alternative interpretations, these results may indicate a reduced vigilance to negative environmental stimuli in subjects who regularly use probiotics. Importantly, the changes in brain activity were not related to self-reported gastrointestinal symptoms, indicating that the central effect observed was not simply a result of an improved sense of digestive well-being.

3.11 Nutritional Psychiatry Research

Diet has emerged as a significant variable among factors that may contribute to resilience against mental disorders or, conversely, pose a risk (Sarris et al. 2014). At a glance, nutrition appears to be a self-explanatory variable in terms of its mechanistic potential. The brain, functioning at a high metabolism, consumes a significant portion of the body's energy and nutrient intake. Amino acids, fats, vitamins, minerals, and trace elements are crucial for the brain's structure and function, including intra- and intercellular communication. The antioxidant defense system, crucial in psychiatry (Moylan et al. 2014), relies on nutrient cofactors and phytochemicals. The immune system, vital in psychiatric disorders, is significantly impacted by lifestyle aspects and diets (Berk et al. 2013). Nutrition has substantial importance in influencing nerve development and repair (neurotrophic factors) all over life (Sizonenko et al. 2013). Essentially, a theoretical outline of the biological mechanisms through which nutrition can express its effect, ranging from general mental well-being to neuropsychiatric disorders, is very conceivable. Despite its fundamental importance in physiological processes, the impact of nutrition on promoting

or counteracting positive mental health has faced neglect and suffered from inaccurate studies with poor designs that make it difficult to interpret data.

Promisingly, there are signs of a significant shift in nutritional considerations in mental health, and given the previous discussion of the burden of mental illness, this development is appropriate. Numerous epidemiological studies, including well-designed prospective studies, have demonstrated a link between adherence to healthy dietary patterns and a reduced risk of anxiety and/or depression (Jacka et al. 2011; Rienks et al. 2013; Psaltopoulou et al. 2013). The findings from these studies have clinical relevance rather than mere statistical significance, and indicate that nutrition can be more flexible and provide meaningful outcomes.

Recent research has associated healthy dietary patterns, characterized by a high consumption of vegetables, potatoes, fruits, soy products, mushrooms, sea foods, and seaweed, with a decreased risk of suicide (Nanri et al. 2013). Specific elements within the diet, such as green tea and coffee, have also been linked to a reduced risk of depressive symptoms (Pham et al. 2014). In addition, nutrition is gaining recognition as a critical factor within the Developmental Origins of Health and Disease (DOHaD) framework. Early nutrition is convincingly associated with later mental health outcomes (Jacka et al. 2013). Furthermore, adherence to a Mediterranean diet in later stages of life has been shown to lead to improved cognitive outcomes and a lower risk of dementia (Solfrizzi and Panza 2014; Martínez-Lapiscina et al. 2013).

3.12 Nutritional Neuroscience Research Design and Control

Undoubtedly, the significance of the presence of study control in the design and execution of behavioral research concerning nutritional elements could not be overstated. Given that the impacts of dietary interventions are often relatively subtle, it becomes imperative to meticulously control all extraneous variables. Crucial components of experimental control in nutritional studies encompass the implementation of double-blind procedures, incorporation of placebo drugs, and meticulous standardization and control of every facet of the testing environment. Additional vital factors involve securing an ample sample size, choosing pertinent behavioral tests, adopting a conservative stance in data analysis, generating dose-response functions and interpretation, and replicating results both across and within different laboratories.

Because of humans' susceptibility to subtle cues from their environment, especially the behavior of other individuals, maintaining uniformity in the physical and social aspects of the testing environment is critical in studies involving nutritional factors. Examiners need careful training to deal with any test-related issues consistently and professionally, to ensure uniformity in their approach. Instructions provided to volunteers must be standardized, and if feasible, the same investigator or team should be responsible for testing all subjects in a given study. Environmental conditions, including factors like time of day, temperature, humidity, and light levels, should be kept constant and under experimental control. Moreover, testing

equipment should be identical for all subjects to enhance the reliability and validity of the study.

The selection of suitable behavioral tasks for detecting the impacts of food constituents on human mood and behavior is a critical aspect in the design of these studies. Despite the availability of numerous standardized behavioral tasks and mood questionnaires, determining the most appropriate tool to assess a specific parameter is a topic of considerable debate.

3.13 Conclusion

Human Nutritional Neuroscience is a rapidly evolving field that has important implications for brain health, cognitive function, and mental well-being. This paper has explored some of the fundamental issues in this field, including the effect of nutrition on the health of brains, the gut-brain axis, and mental health. By understanding these issues, we can begin to develop more effective strategies for promoting brain health and preventing cognitive decline and mental health conditions.

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Chapter 4
Central Nervous System Regulation of Eating and Brain Functions

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Abstract Human eating habit is controlled by the central nervous system (CNS), a process that involves a plethora of molecular associations with numerous tissues, neurotransmitters, neural circuits, and hormones. It is governed by the hedonic and homeostatic systems interaction. Hedonic control is orchestrated through conscious and unconscious reward systems, whereas homeostatic control is governed by food-craving signals from the adipocytes, gut, as well as the vagus nerve. On the one hand, the CNS receives powerful food-related feedback via perception of texture, smell, sight, and taste, which in turn affects brain regions involved in reward produced by feeding. Contrariwise, the nutrients essential in relatively large amounts for growth and health makeup increase the gut's release of the hunger signal, which the central nervous system translates into unconsciously rewarding activities. This review considers how physiological impulses from the adipocytes, gastrointestinal tracts, and many more engage sets of interacting neural networks spread throughout the brain to bring about the complex motor occurrences that cause animals to eat in order to address the eating and brain functions by the central nervous system.

Keywords Eating · Brain · Food · Central nervous system · Homeostatic system · Hedonic system

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4.1 Introduction

Eating is among the most crucial motivated activities for maintaining the energy balance of the body. There are three stages of eating: hunger, satiation, and satisfaction. The urge to eat is one definition of hunger. Satisfaction, on the other hand, is the procedure that ends an eating experience. In the postprandial phase, satiation prevents eating (Blundell et al. 2010). The homeostatic as well as hedonic elements of feeding regulation control these dynamic stages. The CNS, which has ultimate control over this process, receives feedback about an individual's metabolic status from several organs and systems that govern food intake.

A meal's beginning, ending, and timing are all influenced by sensible as well as insensible neuro-hormonal mechanisms, most of which originate from the internal environment and others from the external and are interpreted by sight, taste, and smell senses. The homeostatic (also known as metabolic) and hedonic (sometimes known as reward) aspects of food intake are both crucial to this control mechanism. The brain stem and hypothalamus are crucial components of homeostatic regulation. Non-homeostatic regulation has more to do with "hedonic" feeding, which appears as hyperphagia for appetizing meals, than it does with the management of the body's energy balance.

Hedonistic eating is related to the reward components, which include dopamine-producing neurons in the ventral tegmental region. Under physiological as well as pathological circumstances, non-homeostatic and homeostatic systems are coordinatedly regulated. The hypothalamus senses metabolic and visceral input to a large extent in order to regulate homeostasis of food intake (Cifuentes and Acosta 2021). The hypothalamus in the CNS receives messages from the peptides and hormones secreted from the gut in response to meals and the composition of its macronutrients, signals and information from the vagus nerve as well as the adipocytes.

The system consists of leptin and melanocortin in the paraventricular and arcuate nuclei processes and decodes this homeostatic input from the gut, adipocytes, as well as the vagus nerve into onset or offset food intake signals.

Hedonic feeding, which does not involve the person's metabolic condition or the nutritional content of the consumed food, is the process that enables an individual eat only to evoke happy moods and/or to escape from non-pleasurable feelings (Avena 2015). The sensible sensory signals from the qualities of the meal that provide subjective liking insensible process controlled by gut hormones associated with appetite are what make up the pleasurable (hedonic) aspect of food intake. The salience of foods is improved and bolstered by this metabolic process.

Conceptually, hedonic control is used to explain why some foods, regardless of their calorie density, are greatly preferred to others. In addition to leading to calorie consumption above what is required to bring back energy availability close to the energy balance, the desire for certain foods can occur without a perceived or real energy shortage. According to the current theory, hedonic factors interfere with homeostatic controls, leading to great consumption of calorie and ultimately

increase in body weight (Liu and Kanoski 2018; De Araujo et al. 2020). However, just like with homeostatic eating, the intricate relationships between several dispersed regulatory mechanisms defy easy categorization.

4.2 Homeostatic Food Intake

Hormonal, peptides, and visceral information released from the stomach and intestines are the primary drivers of homeostatic regulation. When macronutrients from meal enter the gut lumen, gut hormones like peptide tyrosine tyrosine (PYY), glucagon-like peptide-1 (GLP-1), cholecystokinin (CCK), and ghrelin are secreted in response (Camilleri 2015). In order for these signals to operate as substances that transmit nerve impulses and be translated into brief onset or offset feeding impulses, they must first travel via the bloodstream to the CNS. Leptin performs an essential function in controlling energy balance by serving as an indicator of fullness when it is available but substantially promoting craving or urgent need for food when it is not available, reduced, or improperly perceived (Friedman 2014).

The vagus nerve transmits bodily signals to the brainstem from the gastrointestinal tract, from the brainstem, the signals are interpreted and sent to the hypothalamus (as well as other regions of the brain) (Berthoud 2008). The master controller of desire to eat food and body weight is the brain. A lot of neural systems take part in the complex process of feeding regulation by the brain of human. The hypothalamus performs a vital responsibility in the homeostatic regulation of eating by controlling food intake.

The hypothalamus' arcuate nucleus regulates desire to eat food and contains neurons that express agouti-related protein (ARP) and neuropeptide Y (NPY), which increase desire to eat food and reduce consumption of energy, as well as neurons that express pro-opiomelanocortin (POMC), cocaine- and amphetamine-regulated transcript (CART), which reduce desire to eat food and increases consumption of energy. These neurons are controlled by hormonal signals from the periphery, which act on the hypothalamus to excite or inhibit these neurons and change feeding desire. To regulate eating, orexigenic and anorexigenic neurons in the hypothalamus arcuate nucleus communicate with one another. The hypothalamus is a hub for controlling feeding. More details regarding the control of energy balance by the brain, particularly feeding, have come to light in recent years thanks to the monogenic obesity-linked mutations discovery (Farooqi et al. 2003). It's interesting to note that the majority of genes linked to obesity found expression in the central nervous system, mainly in the regions of the brain related to making decision, memory, and reward (Locke et al. 2015).

Rodents' feeding habits have been demonstrated to be modulated by hypothalamic stimulation. Rats with deep brain stimulation of the lateral hypothalamic nucleus consume less food and weigh less (Sani et al. 2007).

Rodents' feeding as well as their body weights fall when the ventromedial part of the hypothalamus is stimulated (Lehmkuhle et al. 2010). In monkeys, activation of the ventromedial hypothalamus was associated with increased food consumption (Lacan et al. 2008). This disparity reveals possible variations between rats and people in the function of the hypothalamus and its subnuclei in controlling appetite. In order to control eating and appetite, humans appear to use a brain network that is significantly more complex. The entire scenario of the affective and cognitive circuitry involved in dysregulated feeding in man may not be well captured by this mechanism, despite the fact that dysregulated homeostatic regulation of food may play a role in the development of obesity. Human studies on the hypothalamus' function in controlling hunger and eating have yielded few results. In human fMRI research, activation of the hypothalamus, midbrain, striatum, and thalamus, in response to a milkshake predicted weight growth within a year (Geha et al. 2013). In humans, the hypothalamus activation may be subject to control by these higher systems because it receives external messages, and directly communicates with parts of the reward, emotion, and memory components, as well as with the areas concerned with cognition and other cortical areas through the thalamus. Consequently, although the hypothalamus is crucial to the homeostatic regulation of eating, it might be controlled by a number of other component systems when deciding how much food to consume.

4.3 Brain Networks Involved in Eating

There has been significant evidence linking several brain areas, cell types, and even particular projections to the control of feeding. The increasingly advanced methods of influencing cellular signaling and gene regulatory systems over the past forty years have contributed significantly to our knowledge of how the brain regulates eating behaviors. For the past 15 years, these researches have dominated the field, in especially those that use mouse genetics. However, this has come at the expense of some of the more thorough behavioral analyses. It is understandable that the current emphasis of these genetically targeted manipulations is more on food consumption than the more general aspects of eating behaviors, but it is expected that these approaches will eventually be focused on exploring how complex the appetitive actions, behavioral switching, meal patterns, etc. that make up eating behavior. This latest molecularly focused finding has continued to highlight a very few brain regions, building on the foundation of what was formerly known as physiological psychology. The arcuate (ARC) nuclei in the hypothalamus, the nucleus of the solitary tract (NST), the parabrachial nucleus (PBN), the ventromedial hypothalamus (VMH), the dorsomedial hypothalamus (DMH), and the paraventricular nuclei (PVN) are among these.

4.4 Arcuate Nucleus

The ARC nucleus consists of two main populations of neurons: the population that express the anorexigenic neuropeptides proopiomelanocortin (POMC), cocaine- and amphetamine-regulated transcript, and another subset that produce the agouti-related peptide (ARP) and orexigenic neuropeptides neuropeptide Y (NPY). According to Schwartz et al. (2000), they are the first set of neurons on which hormones that take part in metabolic activities, such as insulin, ghrelin, and leptin, largely act.

POMC neurons transmit axonal processes to preganglionic neurons in the brain stem, spinal cord as well as to a second set of neurons in hypothalamic regions which include the ventromedial hypothalamus (VMH), paraventricular nucleus (PVN), and lateral hypothalamus (LH) (Bouret et al. 2004). The ARC nucleus, which is situated at the ventral surface of the hypothalamus, and right above the fenestrated hypophyseal system, is in a great location for integrating endocrine and external signals.

4.5 Paraventricular Nuclei

Dietary restriction strongly activates ARP neurons via glutamatergic afferents (Liu et al. 2012). The paraventricular hypothalamic nucleus (PVH) is a significant source of excitatory input, and its activation promotes eating via an ARP neuron-dependent mechanism (Krashes et al. 2014). Additionally, even only the sensory input of food can quickly suppress ARP neurons (within seconds) (Mandelblat-Cerf et al. 2015; Chen et al. 2015). According to Garfield et al. (2016), this action may be caused by inhibitory signals from the PVH that are enough to prevent feeding caused by hunger.

ARP neurons then combine messages from hormonal secretions from tissues with excitatory and inhibitory inputs. Appropriately, ARP neurons can sustain and add changes in membrane potential for a long duration, demonstrating astounding long-term integration of inputs (Branco et al. 2016). This could be an adaptive system to control appetite continuously and variably. According to Stachniak et al. (2014), ARP neurons' effects on driving feeding are best understood when they project to the PVH and anterior bed nucleus of the stria terminalis, periventricular thalamus, and the lateral hypothalamic region (LHA). Proopiomelanocortin (POMC), the pro-hormone which is converted to endogenous melanocortin receptor agonists, is expressed by another significant ARC neuronal population that regulates energy balance. Inhibition of food intake by POMC neuron activation occurs over longer time periods (a few hours as opposed to minutes) than the effects of ARP neuron activation (Aponte et al. 2011). The actions of glutamatergic efferents from the ARC to the PVH are amplified by the POMC derivative,

α-melanocyte-stimulating hormone (α-MSH), which is consistent with their neuropeptidergic character (Fenselau et al. 2017). It's amazing that serotonin (5-hydroxytryptamine; 5-HT) and noradrenaline both regulate ARP and POMC neurons, which coexist inside the ARC and have opposing effects on hunger.

4.6 Lateral Hypothalamic Area

The LHA is referred to as the feeding center because parts of its neurons participate in the regulation of eating. According to Suber and Wise (2016), the LHA and perifornical area's melanin-concentrating hormone (MCH) neurons as well as orexin neurons are activated, increasing the intake of food. The ARC's POMC and NPY/ARP neurons control the activity of these neurons. The motivated behaviors as well as the sleep-wake cycle are both regulated by orexin neurons and MCH neurons, among other things (Sakurai 2014). A few GABAergic and glutamatergic neurons in the LHA have also been found to control feeding in addition to MCH and orexin neurons (Sakurai 2014), with glutamatergic neuron activation increasing food intake while GABAergic neuron activation decreases it. The ventral tegmental region of the LHA, which interacts with dopaminergic neurons that connect to the striatum and nucleus accumbens, makes it a distinctive hypothalamic region (Sakurai 2014). The reward system is regulated by glutamatergic and GABAergic neurons in the LH. Given that its destruction can cause hypophagia and weight loss, LHA is thought of as a feeding center. Melanin-concentrating hormone (MCH) and orexin, orexigenic neuropeptides, are produced by two populations of neurons in the LH. Neurons that express MCH and orexin are in touch with NPY/ARP- and immunoreactive terminals of α-MSH from ARC neurons.

4.7 Parabrachial Nuclei

Two mechanisms can be used to stop eating. To control the physiological cycle of feeding, one is regulated by satiety signals, while the other is controlled by anorexic inputs like cancer cachexia or abdominal pain. Both of these mechanisms include the PBN (Wu et al. 2012; Palmiter 2018; Cheng et al. 2020). Afferent nerve fibers in the vagus nerve, the NST, and subsequently the PBN-mediated gut-related neural signals reduce food intake. Recent research has shown that satiety impulses are transmitted by non-calcitonin gene-related peptide (NCGRP) PBN neurons while anorexic impulses are transmitted by calcitonin gene-related peptide (CGRP) expressing neurons in the PBN (Palmiter 2018; Cheng et al. 2020). Through a GABAergic signal, NPY/ARP neurons in the ARC hinder CGRP neurons in the PBN (Wu et al. 2012). By activating the CGRP neurons and stopping feeding, the removal of these NPY/ARP neurons in adult mice causes extreme hunger and death. The mice can continue feeding and survive, however, when GABA is injected into the PBN.

4.8 Nucleus of the Solitary Tract

Another important brain part that performs function in controlling appetite is the brain stem. The sensory part of the vagus nerve, a crucial connection between the brain and gut, transmits satiety signals from the gut to the nucleus of solitary tract (NST). The area postrema is another circumventricular organ, and it has physical proximity with the ARC (Stanley et al. 2005). Because of this, the NST is well positioned to pick up both neurological and humoral impulses. According to Geerling et al. (2010), the NST and PVN get substantial projections of neurons from each other, demonstrating the brain stem and hypothalamus close connectivity. Similar to the neurons of the hypothalamus, neurons of NST also monitor peripheral metabolic signals and produce the hormones that control appetite, NPY, glucagon-like peptide-1(GLP-1), as well as POMC (Ahima and Antwi 2008). For instance, in response to exogenous leptin, NST POMC neurons were involved in transduction of signal and stimulation of transcription 3 (STAT3) activation (Ellacott et al. 2006). As a result, nutrients and circulating hormones may influence the hypothalamus as well as the brain stem, relaying signals of metabolic activities to the brain. Findings have shown that feeding activates NST's neurons, particularly those that produce cholecystokinin (CCK) (D'Agostino et al. 2016; Roman et al. 2016). It is enough to activate these neurons to reduce appetite. Similar to inhibiting PBN output, Wu et al. (2012) found that blocking NST-PBN input can prevent starvation brought on by ARP's neuron removal. The NST also integrates serotonergic afferents, whose inhibition can counteract the malnutrition brought on by the ablation of ARP's neurons (Wu et al. 2012).

4.9 Gut/Adipose Tissue Hormones and Peptides Involved in Feeding

The enteroendocrine cells (EECs) are widely dispersed throughout the GIT, and are the main producers of gut hormones. Following food intake, EECs could detect the food nutrients and produce a range of GIT hormones that control energy homeostasis on an autocrine, paracrine, and endocrine level (Latorre et al. 2016). These hormones have strong appetite-regulating properties and alert the CNS (gut-brain axis) when nutrients are available. For food intake, break down of food, secretion by pancreas, as well as control of metabolism, EECs nutrient detection is essential (Bewick 2012). The key hormones of the GIT responsible for the control of energy balance are oxyntomodulin (OXM), peptide tyrosine-tyrosine (PYY), pancreatic polypeptide (PP), cholecystokinin (CCK), ghrelin, glucagon-like peptide 1 (GLP-1), glicentin, and amylin (Wynne et al. 2005; Karra and Batterham 2010). All these hormones are anorexigenic except ghrelin which is orexigenic. The hypothalamus is leptin's major site of action in the CNS. Leptin is released by white adipocytes and is connected with the adiposity level (Hussain and Khan 2017). In the energy

balance, leptin's main function is stimulation of extreme desire for food as a result of low or reduced amount of the hormone in the blood. Leptin deficiency is perceived by the CNS as an energy deficit state, which prompts compensatory actions like increased hunger and decreased resting energy expenditure (Flier and Maratos-Flier 2017). It's interesting to note that after 48 h of caloric restriction, leptin levels abruptly dropped, demonstrating that leptin controls the energy balance in an immediate manner without affecting weight or adiposity (Collet et al. 2017). Leptin hinders the ARP/NPY-expressing neurons through a significant reduction in the expression of cytokine signaling 3 and activation of POMC/CART-expressing neurons in the hypothalamus arcuate neurons (ARC) through a rise in c-Fos levels.

4.10 Orexigenic Gut Hormones

The ARC and the part of the stomach known as gastric fundus contain oxyntic glands that release the orexigenic peptide ghrelin (Muller et al. 2015). Prior to a meal, ghrelin is produced and is regulated by insulin-induced hypoglycemia, weight loss, cephalic-phase reflexes, and fasting. Ghrelin activates the production of ARP and NPY to prevent melanocortin receptor 4 (MC4R), which is expressed in the PVN, enhancing feeding, as well as hindering the impacts of POMC neurons. Ghrelin receptors are seen in ARP/NPY-expressing neurons in the ARC of the CNS. Ghrelin is well known to affect reward-related brain regions in fMRI experiments, which suggests that it promotes food intake by making food more pleasurable. Making decisions, being motivated to eat, and exerting physical effort to gain energy resources all depend on food rewards. Dopamine activity rises in the nucleus accumben in response to ghrelin injections given to rats in the ventral tegmental region (VTA), which encourages the animal to exert more effort to receive the food-related reward (Skibicka et al. 2013). Additionally, memory and learning functions in mice have been linked to the secretagogue receptor 1a which is a growth hormone (Albarran-Zeckler et al. 2011). Ghrelin is important as a connector between the hedonic and homeostatic systems in the control of feeding. An fMRI finding conducted on human participants revealed that administration of ghrelin caused a rise in reward prediction error signaling in structures of dopamine and promoted conditioning of food odor (Chin et al. 2018). Similar to a fasting state, ghrelin heightens hunger pangs as well as the food's pleasurable qualities (Prechtl de Hernandez 2011).

4.11 Anorexigenic Gut Hormones

Peptide tyrosine-tyrosine (PYY) contains 36 amino acids. In response to ingestion of food, the distal gut L-cells predominantly produce PYY. According to Helou et al. (2008), calorie intake, meal consistency, and macronutrient composition can

all have an impact on circulating levels of PYY. Within 15–30 min after consuming food, the initial increase in circulating levels of PYY is often seen. The levels of PYY reach their peak 1–2 h after eating food, followed by an extended plateau phase. By stimulating the vagus nerve, PYY decreases eating desire and consumption of energy, slows emptying of gastric, and stimulates secretion of insulin (De Silva et al. 2011). PYY3–36 administration (peripheral) has been demonstrated to decrease feeding and body weight in rodents (Vrang et al. 2006), as well as in lean and obese people (Sloth et al. 2007). In comparison to their lean counterparts, obese people have decreased fasting PYY circulating levels, and their meal-stimulated PYY production is attenuated (Steinert et al. 2017). As a result, they need more calories than people of normal weight need to reach a similar postprandial PYY concentration (Batterham et al. 2006). In response to luminal nutrients, L-EECs in the colon and ileum secrete glucagon-like peptide-1 (GLP-1) (Psichas et al. 2015), but few group of neurons in the NST can also secrete GLP-1 (Campbell and Drucker 2013). GLP-1 slows down stomach emptying, lowers glucagon secretion, and boosts glucose-dependent insulin release. Through its receptors found in the NST, ARC, area postrema (AP), and PVN, it also decreases food intake (Parkinson et al. 2009). According to Van Bloemendaal et al. (2014), GLP-1's anorexigenic effects are connected to its effect on regions of the brain which control the food hedonic qualities. I-enteroendocrine cells (EECs), which are mainly found in the proximal jejunum and duodenum, release cholecystokinin (CCK). The amount of fat in a meal mostly stimulates its secretion. CCK serves as a neurotransmitter and has receptors in the thalamus, hypothalamus, dorsal hindbrain, cerebral cortex, and basal ganglia (Little et al. 2005). CCK decreases meal size and particularly signals satiation. Additionally, consuming a fat-rich diet raises the levels of CCK that are inversely linked with the actions of the brain regions which are associated with taste and reward (Eldeghaidy et al. 2016). In addition, it has been shown that after a high-fat load, CCK-dependent activation occurs in CNS areas such as the anterior cerebellum, posterior cerebellum, and motor cortex (Lassman et al. 2010). In reaction to eating, the beta cells of pancreas release insulin and amylin (islet amyloid polypeptide). According to results from imaging, behavioral, and electrophysiological investigations, amylin largely inhibits eating through acting on the region postrema (Boyle et al. 2018). Amylin also affects neurons of ARC/POMC, where it strengthens leptin's impact. Additionally, amylin lowers blood sugar levels through its combined effects on nutritional absorption, stomach emptying, feeding, and digestive secretions. Boyle et al. (2018) stated that the amylin analog pramlintide is a recognized diabetes medication that also combats obesity. One of three receptor activity-modifying proteins (RAMP1–3) and calcitonin receptor (CTR) are combined in an unusual way by the amylin receptor. The CTR's affinity for amylin is markedly increased by these RAMPs, effectively converting it to an amylin receptor. The NST, the lateral parabrachial, the central amygdala, and maybe the bed nuclei of the terminal stria are all parts of an ascending neuronal pathway that are activated when amylin binds to its receptors in the AP.

4.12 Feedback Signal from Visceroceptive Regions

Visceral messages coming from the gut are carried by the vagus nerve (X). The homeostatic control of food intake depends on this knowledge. Efferent signals coming from the vagus nerve affect the secretion and movement in the GIT, pacing the absorption of nutrient's rate, mobilization, and storage of food. Exterior muscle layer's afferents which are responsive to tension and stretch tell about the quantity of swallowed foods, whereas vagal afferents which are sensitive to mechanical stimulus in the mucosa layer of the stomach find out that foods have been eaten (Berthoud 2008). It's interesting to note that the vagus nerve provides feedback on gastric distension to brain cells that process taste in the somatosensory cortex's visceral region. This suggests a potential method through which feeling full affects perception of taste. Vagus nerve's feedback assists with meal quantity, commencement, timing, and termination by providing information about food qualities to hedonic and homeostatic brain regions. Feeding is controlled by visceroceptive input from vagal afferents by engaging brain regions related to sensorimotor activities, taste, pain, and aversion. Furthermore, the hormones of the GIT released as a result of the food's highly essential nutrient component increase the anorexigenic effects of the mechanical stimulus that food produces.

4.13 Regulation of Eating by Hypothalamus

The Leptin-Melanocortin Hypothalamic Pathway: The first channel through which metabolic impulses from the peripheral parts are initially detected as well as converted into anorexigenic and orexigenic signals to control energy equilibrium is the hypothalamic nuclei. The ARC is situated around the ventral third ventricle and is surrounded by a semi-permeable blood-brain barrier (BBB) created by a network of capillaries which consist of many openings that permit impulses to reach the central nervous system. The anorexigenic group of the ARC is represented by the neurons that express POMC/CART, albeit they are also found in the NST. On the other hand, the orexigenic ARC's group is made up of ARP/NPY neurons. Despite having opposing functional properties, there is co-expression of receptors and comparable efferent linkages to the forebrain between the ARP/NPY and POMC/CART neurons (Wang et al. 2015). POMC is broken down into N-POMC, β-lipotropic hormone (β-LPH), and adrenocorticotropin hormone (ACTH) in the anterior lobe of the pituitary gland.

But, β-LPH and ACTH are subsequently broken down in the ARC to produce melanocyte-stimulating hormones (α-MSH, β-MSH), respectively (Harno et al. 2018). Leptin as well as some homeostatic peripheral impulses like PYY and GLP-1 cause the secretion of α-MSH. Nevertheless, they too are excited by expected sensory food signals and seem to stay active for a considerable amount of time after the

stimuli have been eliminated (Chen et al. 2019). Ghrelin activates ARP/NPY neurons, whereas PYY and leptin suppress them.

ARP/NPY neuron activation promotes eating, and experiment with rodents has demonstrated that craving or urgent desire for food is perceived as an unpleasant emotion. The ARC, which stands for the downstream hypothalamic structure in the leptin-melanocortin pathway, is situated dorsal to the PVN. AgRP/NPY neuron activation promotes food intake, and rodent models have demonstrated that hunger is perceived as an unpleasant emotion. Accordingly, there was a proposition that the gratifying impact of eating stems from the elimination of this unpleasant feeling of hunger, which makes eating a positive experience (Betley et al. 2015). AgRP/NPY neuron density in humans is inversely linked with body mass index (BMI) (Alkemade et al. 2012). The orexins and melanin-concentrating hormone (MCH), which are hypocretins, mediate the orexigenic actions of the LHA Hypocretin Pathway. These hypocretin-secreting neurons are interconnected with other brain regions and share connections with them. The reticular activating system and the brainstem receive protrusion from orexin and MCH neurons. The medulla as well as the spinal cord's projections to autonomic regions help to control the secretion of pancreatic hormones, stomach motility, and saliva. The monoaminergic arousal system is also linked to the hypocretin system. Neurotransmitters like serotonin and dopamine serve as the link between the reward system and the LHA in the monoaminergic system. A foundation for understanding how hypocretins affect the control of feeding could be provided by the locations in which they are projected.

4.14 Control of Hedonic Feeding/Neurotransmitters and Neuropeptides Involved

Hedonic eating relies heavily on the dopaminergic system. A crucial neurotransmitter that can control reward is dopamine (DA). The DA has opposing impacts on eating in two key areas, the LHA and VMH. The concentration of DA in the LHA region rose right after the food intake, stayed above the normal level throughout feeding, but returned to normal once it was finished. Dopamine levels rise during fasts and fall after meals in the VMH area, in contrast. In contrast, reward processing in response to food stimuli has been linked to the function of DA in the mesolimbic/mesocortical region (Berridge et al. 2009). Dopamine neurons fire in bursts in response to environmental stimuli, releasing phasic DA thereafter. Specific behaviors, such as "wanting" food, will be motivated by this increase in DA signaling (Volkow et al. 2011). However, the "liking" of the food appears to be enhanced by the stimulation of the cannabinoid and opioid systems, which appears to stimulate in part. Despite being distinct, the brain reward systems involved in eating behavior work together to control food intake (Volkow et al. 2011). Additionally, serotonin (5-HT) has been linked to the regulation of eating (Voigt and Fink 2015).

To increase satiety, 5-HT interacts with central melanocortin neurons in the hypothalamus. According to Wyler et al. (2017), 5-HT2c receptor stimulation elevates the activity of anorexigenic neurons of POMC while 5-HT1b receptor activation suppresses orexigenic NPY/ARP neurons. Serotonin integrates peripheral satiety signals in the NST (Voigt and Fink 2015).

4.15 Dopamine

DA is among the highly researched neurotransmitters in the control of feeding. The principal dopaminergic network of interconnecting neurons in controlling appetite is the pathway of mesolimbic system, which extends through the VTA to the striatum, the dorsal (which includes the putamen and caudate nucleus), and the ventral (which includes the olfactory tubercule and the NAc). DA's function is frequently unduly or extremely simplified as the main neurotransmitter engaged in the control of reward, despite its extensive participation in the regulation of hedonic eating (Coccurello and Maccarrone 2018). DA- and 5-HT-related brain functions are quickly vulnerable to tolerance after repeated exposure. This tolerance reward in feeding results in a finding action that seeks out new food stimuli to re-experience reward (Epstein et al. 2009). Obesity, variability, and the amount of calorie intake are critical predictors of eating behavior and are influenced by food reinforcement (via reward mechanisms) and habit (Epstein and Carr 2021). Despite this tolerance or addiction, pleasant stimuli from DA are translated into expected signals (such as the thought, smell, or sight of food) that predict reward, and eventually become conditioned actions. However, as previously mentioned, the degree of reward of a particular meal type is dependent on whether it is palatable or not, and other factors including economics, availability, socio-cultural context, incentives, and whether it is appealing to the eye or not. Some foods, particularly high fat- and high sugar-containing foods, can cause addiction (Avena et al. 2009).

4.16 Serotonin

The gastrointestinal and central nervous systems both produce the biogenic amine 5-HT. The midbrain, cerebellum, pons, spinal cord, and the medulla receive caudal protrusion from groups B1 to B4 in the raphe nuclei, whereas the cerebral cortex, striatum, amygdala, and hypothalamus receive ascending projections from populations B5 to B9 (Berridge et al. 2010). 5-HT levels are inversely proportional to food consumption and are linked to mood, cognition, autonomic, and homeostatic function (Berridge et al. 2010). Using primarily SPECT and PET with radioligands of 5-HT, the majority of neuroimaging findings examining 5-HT's function have been

carried out in individuals with feeding abnormalities (such as bulimia nervosa and anorexia nervosa) (Kranz et al. 2010). The density of serotonin receptor 4 (5-HT4R) in the ventral pallidum and nucleus accumben (NAc) was found to strongly correlate with BMI in a finding utilizing PET in obese persons, indicating an overexpression of 5-HT4R in these regions (Haahr et al. 2012). Another fMRI study that looked at the relationship between 5-HT and prediction of reward found that, at both short- and long-term scales, the activity of 5-HT in the dorsal and ventral striatum corresponded with prediction of reward (Tanaka et al. 2007). The results led the authors to the hypothesis that the striatum's 5-HT activity regulates the temporal scale of reward prediction. Additionally, satiation increased while hunger and palatable food consumption decreased (Thomas et al. 2017).

4.17 Endocannabinoid and Opioid System

The "liking" process in eating is regulated by the endocannabinoid as well as opioid circuitries (Rahman et al. 2021). 2-arachidonoylglycerol (2-AG) and Anandamide, also referred to as N-arachidonoyl ethanolamine, are two of the most noteworthy endocannabinoids, and are produced from arachidonic acid's lipid derivatives; they act on the CB1 receptor (CB1R). Big rats which are deficient in diacylglycerol lipase isoform α (DGL-α), a protein that takes part in the diacylglycerol biotransformation to 2-AG, exhibit reduced eating behavior and a thin physical appearance, pointing to a possible clinical use of DGL-α blockage in obese persons (Piomelli and Tagne 2022). Nevertheless some endocannabinoid-related compounds, like oleoylethanolamide (OEA), likewise play a significant influence in controlling food intake, especially in the satiation process (Rahman et al. 2021). The extended system of endocannabinoid, also known as the endocannabinoidome, is made up of endocannabinoids, endocannabinoid-like compounds, their enzymes, and receptors (Veilleux et al. 2019). It has been suggested that the endocannabinoidome is controlled by dietary fatty acids, that it has an effect on the microbiota, and that it regulates food intake through these interactions (Sihag and Di Marzo 2022). The opioid receptors μ, κ, and δ, as well as β -endorphins, enkephalins, and dynorphins make up the inner network of opioid in the CNS. The opioid receptor μ is a key player in the control of eating, especially when it comes to the rewarding and motivating qualities of food and food-related cues (Peciña and Smith 2010). In conclusion, the endocannabinoid system works as a powerful controller of feeding by raising the degree of hunger, albeit with significant impacts on mood. In addition, orexigenic endocannabinoid-like chemicals have the opposite impact on controlling eating. By its actions on the stomach, nutrition, as well as micro-organism living in or on human bodies, the expanded endocannabinoid system appears to perform a substantial function in regulating eating.

4.18 Homeostatic and Hedonic Systems Cross-Talk

The neurochemical underpinnings of the homeostatic and hedonic systems interact with one another (Berthoud et al. 2017) in which the desire for food is affected by satiation or food scarcity. It's interesting to note that insulin, ghrelin leptin, and GLP-1 all directly affect the mesocorticolimbic dopamine pathway, mediating this cross-talk (Jerlhag et al. 2012). Insulin can stimulate some brain receptors (negative feedback) in addition to acting peripherally by promoting energy storage, which reduces mesolimbic dopamine networks activity and, as a result, food reward (Mebel et al. 2012). According to Farr et al. (2016), GLP-1 signaling in the mesolimbic pathway could selectively lower the tasty food's reward value. In reward-related circuits, ghrelin also performs a significant function in enhancing the response of brain cells to food images (Malik et al. 2008). Accordingly, the mesoaccumbal dopamine pathway as well as the reward gotten from appealing meal can be activated by ghrelin, an orexigenic hormone gotten from the stomach, when signaling increases (Egecioglu et al. 2011). In addition to the direct interactions identified between the two systems, different protrusion from the LH to the VTA, which include glutamate-, gamma-aminobutyric acid (GABA)-, and orexin-expressing neurons, also have indirect effects (Nieh et al. 2016). The biological system of man offers countless neuroendocrine actions for controlling eating, and modulating the symptoms of fullness and hunger. Its control is extremely intricate and involves numerous interactions of molecules with hormones, numerous tissues, as well as neuronal networks. Therefore, for healthy energy balance, signaling smallest particles that influence feeding is essential (MacLean et al. 2017). Additionally, the hedonic and homeostatic circuits collaborate to increase eating during deprived condition but decrease it during periods of fullness or satiety. According to Volkow et al. (2011), disruption of the connection between the two circuits could encourage the emergence of eating disorders (EDs) including binge eating disorder (BED) and bulimia nervosa (BN) as well as the occurrence and/or exacerbation of obesity. Globally, there has been a reported rise in EDs, abnormal eating conditions such as weight control practices, and binge eating, linked to obesity and EDs (Pike and Dunne 2015).

4.19 Conclusion

The CNS's involvement in the homeostatic and hedonic control of eating is highlighted in this review. Both systems interact, in contrast to the earlier assertion of a divergent, separate control. A further insight into the function of reward mechanisms in the brain that control an important mechanism in human's and other animals' energy intake is provided by the knowledge that the food's nutritional qualities involuntarily modify the brain's reward network via the GIT's hormones. Despite

the remarkable advancements in neuroimaging of human body, the neural composition intricacy, systems, and stages that control eating necessitate more complex experimental set-up to evaluate these factors both together as well as separately in order to fully comprehend this complex control.

Scientists will be able to create preventative measures, explanations for certain disorders, and treatments once they have a better understanding of the complex network that controls food intake. The physiology of incretin in persons who have difficulty in gaining weight or people who remain slim for a protracted period of time after they have initially lost weight are two unresolved problems that require further study to be addressed.

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Chapter 5
Implicated Pathways in Diet and Mental Illness

Waleed M. Foad and Walaa H. Foula

Abstract Health and general well-being have been related to good nutrition and diet. More in-depth review will be given in this chapter to the pathways and mechanisms relating nutrition and diet to mental illness, going further than the generally known diet-related problems. While traditional associations with obesity, heart disease, and diabetes are recognized, many recent scientific evidences back up the concept that diet strongly affects the state of mental well-being, including depression, anxiety, and cognitive function. This review delves into key pathways implicated in the diet-mental illness connection, emphasizing the roles of the gut microbiome, inflammation, oxidative stress, nutrient deficiencies, food sensitivities, disrupted energy metabolism, and neurotransmitter pathways.

Acknowledging the complexity of mental illnesses influenced by genetic, environmental, and lifestyle factors, the chapter highlights the evolving role of diet in mental health research. Current knowledge on how diet influences pathways associated with mental health is critically examined, with a focus on the integration of dietary approaches in neurology and psychiatry. The chapter underscores the recognition of food as a potential modulator of mood and neurological conditions, offering insights into the preventive and therapeutic implications for mental illness.

Keywords Mental well-being · Inflammation pathways · Neurotransmitters · Nutrient deficiencies

5.1 Introduction

Mental illness is a major global health issue, with millions of people affected each year. Depression, anxiety, and other mental illnesses are complex conditions that can be related to a range of genetic, lifestyle, and environmental factors. Recently, diet has been proved to be a potential factor in the development and management of

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mental illness. Research has shown multiple pathways through which diet casts its shadows on some mental illness. An updated scientific review will be discussed in this chapter, highlighting the implicated pathways in diet and mental illness and the increasing integration of dietary approaches in neurology and psychiatry, leading to the recognition of food as a potential modulator of mood and neurological conditions.

5.2 Gut Microbiome and Mental Illness

The gut microbiome is the collection of microorganisms that live in the gastrointestinal tract. This microbiome interacts and significantly affects digestion, absorption of nutrients, and immune system function. The human gut microbiome consists of various microorganisms, including bacteria, viruses, yeast, bacteriophages, and protozoa.

Bacteria are the most extensively studied among gut microbiota. Gram-positive Firmicutes and gram-negative Bacteroidetes predominate the gut microbiome. Different enterotypes within the microbiota have been identified, each sharing high functional uniformity regardless of host characteristics. The majority of microorganisms reside in the colon, synthesizing some beneficial products to the host, including vitamins, essential amino acids, and short-chain fatty acids (SCFAs) maintaining gut wall integrity, regulating both local and systemic immunity.

The gut-brain axis is a two-way communication system between the gut microbiota and the brain (Fig. 5.1), which regulates also other aspects like hormone release, specific immune responses, and some neuronal modulations. This regulation influences the permeability of the intestinal epithelium and the blood-brain barrier. The gut microbiome can affect the levels of neurotransmitters such as gamma-aminobutyric acid (GABA), dopamine, and serotonin, which are involved in mood regulation. The gut microbiome can elicit an inflammatory state, which is also implicated as a pathway in the development of mental illnesses such as depression and anxiety.

In the systemic review conducted by Valle et al. (2023) to investigate the association between mental illnesses and gut microbiota, two databases were searched, PubMed and Scopus, and followed the PRISMA guidelines. The included studies were original research conducted on humans with a control group, and their quality was assessed using the Critical Appraisal Skills Program (CASP). This review revealed a consistent association between psychiatric illnesses and different bacterial phyla. The studies reviewed demonstrated differences in the gut microbiota composition between individuals with mental illnesses and healthy controls. Specifically, a significant relationship between depression, anxiety, stress, eating disorders, autism spectrum disorder (ASD), and the composition of the gut microbiota. The findings suggest that individuals with psychiatric disorders exhibit a disturbance in the pro-inflammatory and/or fermentative taxa, which may exacerbate these pathologies. The dysbiosis of the gut microbiota in mental disorders is

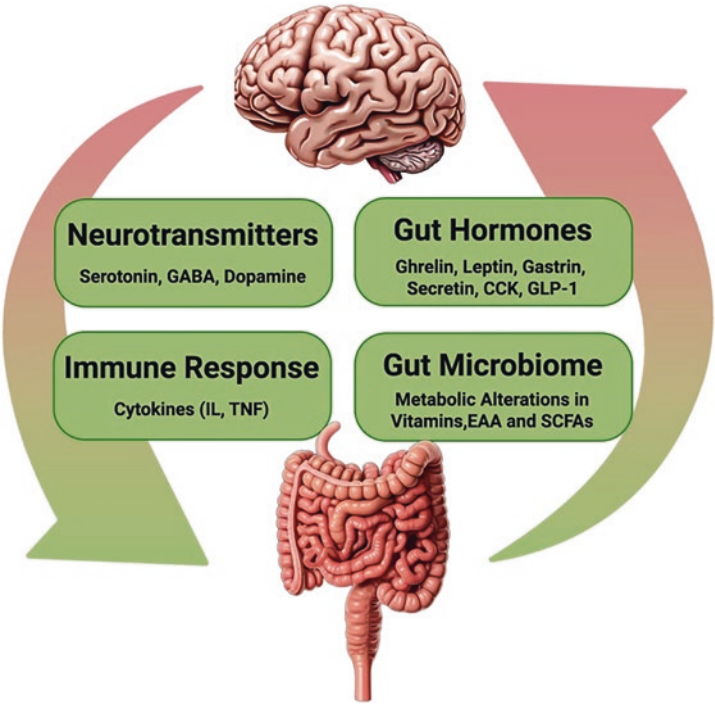

Fig. 5.1 Two-way communication system between the gut-brain axis. *GABA* gamma-aminobutyric acid, *IL* interleukin, *TNF* tumor necrosis factor, *SCFAs* short-chain fatty acids, *CCK* cholecystokinin, *EAA* essential amino acids, *GLP-1* glucagon-like peptide-1

associated with imbalances in neurotransmitters, together with some disturbances in the immune, metabolic, and endocrine systems.

The study also dives into the connection between gut microbiota and specific psychiatric illnesses. It highlights the link between symptoms of autism and gut microbiota dysbiosis. A potential role for the gut microbiota composition in the pathophysiology of depression is suggested, due to the significant difference that was found in gut microbiome in individuals with depression compared to healthy controls. In schizophrenia, dysbiosis has also been considered as a comorbidity of and has been associated with the severity of psychotic symptoms. Also disrupted gut microbiome contributed to metabolic alterations in anorexia nervosa patients.

Furthermore, the study suggested that gut microbiota dysbiosis may contribute to a decline in cognitive function with age, wasting of muscles, and neurodegenerative diseases.

The gut microbiome is significantly modified by diet, as Singh et al. (2017) showed with experiments on changes in microbial composition occurring within a 24 h window after dietary modifications. These findings open new therapeutic possibilities for dietary interventions. It is noted that a high-sugar or high-fat diet can break the normal rhythm of the gut microbiome.

A relatively stable gut microbiome of a healthy individual can be influenced by environmental and dietary factors. Healthcare practitioners and patients can gain better therapeutic outcomes if they are provided with a better understanding of the effects of different dietary components on the gut microbiota.

Severe stress and inflammation can induce rapid alterations in the gut microbiota, sometimes within the same day. Inflammatory bowel diseases (IBD) are associated with reduced bacterial diversity, fewer Bacteroides and Firmicutes, and decreased concentrations of microbial-derived butyrate. The gut microbiota also influences intestinal inflammation and autoimmune arthritis through its effects on immune cell populations and membrane transport. Type 2 diabetes and obesity are also diseases linked to alterations in the gut microbiota, and have subsequent metabolic and behavioral effects.

5.3 Inflammation and Mental Illness

Inflammation, whether acute or chronic, calls on the body's natural response to guard against injury or infection. But chronic inflammation over an extended period of time can be debilitating and can result in many health problems, including mental illness. Research has shown that inflammation is linked to the development of depression, anxiety, and cognitive impairment. Inflammation can affect mood significantly, due to alterations in the levels of neurotransmitters such as GABA, dopamine, and serotonin.

A study by Li et al. (2022) explored the relation between the risk of depression and anxiety and the dietary inflammatory potential. The study utilized a meta-analysis approach to analyze relevant literature and provide an overview of the relationship between diet and common psychological disorders. To assess the inflammatory potential of diet, the authors used the Dietary Inflammation Index (DII), which evaluates the inflammatory potential of diet, according to the pro-inflammatory and anti-inflammatory effects of various dietary components. An anti-inflammatory potential is given a low DII, while a pro-inflammatory potential is given a high DII score. The researchers conducted a systematic literature search in major scientific databases up to February 2021. They included studies that examined the relationship between dietary inflammatory capacity and the risk of anxiety or depression. After eliminating repetitive and irrelevant articles, they performed quality assessment, sensitivity analysis, and publication bias analysis on the selected studies. In total, 17 studies with more than 157,000 participants were included in the final stage of the analysis. The results showed that the highest inflammatory diet group was significantly associated with an increased risk of anxiety and depression, compared to the lowest inflammatory diet group.

Based on these findings, the study suggests that preventive measures for anxiety and depression could include long-term "anti-inflammatory" eating options, while trying to avoid those "pro-inflammatory" eating options that may promote anxiety

and depression. The authors recommend incorporating foods such as fresh fruits, fish, fish oil, and walnuts into the diet.

Diet can influence inflammation in the body. Processed foods and diets rich in sugar, and saturated fat can lead to increased inflammation, while diet patterns rich in whole grains, vegetables, and fruits can reduce inflammation. Omega-3 fatty acids-rich diets, such as salmon, may also reduce inflammation and improve mental health outcomes. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) were shown by Zivkovic et al. (2011) as examples of omega-3 fatty acids, that would reduce the concentrations of cytokines (inflammatory signaling molecules) and adhesion molecules in arterial walls, thereby attenuating the development of atherosclerosis (arterial plaques). Higher blood plasma levels of omega-3 fatty acids have been related to reduced risk of mental disorders such as schizophrenia, and depression and some neurodegenerative diseases like Alzheimer's.

5.4 Oxidative Stress and Mental Illness

Oxidative stress is described as a condition that causes imbalance between oxidant substances produced during metabolism and the body's antioxidant defense mechanisms. This imbalance leads to the accumulation of free radicals, or reactive oxygen species (ROS), which can cause cell damage and various pathological processes. These reactive species are generated through many physiological and pathological processes, such as aerobic metabolism, ischemia, inflammation, emotional or psychological stress, and environmental pollution. Free radicals damage cellular membranes with polyunsaturated fatty acids (PUFAs), resulting in lipid peroxidation and subsequent cellular instability. Damage to nervous cells and tissues caused by oxidative stress has been implicated in the development of mental illness.

Tsaluchidu et al. (2008) conducted a PubMed search using the MeSH search term "oxidative stress" along with each diagnostic category from the DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders, fourth Edition, Text Revision). The search revealed scientific proof of increased oxidative stress in several psychiatric disorders, including attention-deficit hyperactivity disorder (ADHD), autistic disorder, mental retardation, Rett's disorder, delirium, dementia, eating disorders, anxiety disorders, amnestic disorders, alcohol-related disorders, hallucinogen-related disorders, amphetamine-related disorders, nicotine-related disorders, opioid-related disorders, schizophrenia and other psychotic disorders, mood disorders, sexual dysfunctions, and sleep disorders. The study suggests that increased oxidative stress is associated with the majority of psychiatric disorders. This finding highlights the importance of maintaining the integrity and functionality of biomolecules through the integration of fatty acids and antioxidants. The authors propose that fatty acid supplementation may provide some benefit to individuals with psychiatric disorders characterized by increased lipid peroxidation, preferably in combination with an antioxidant-rich diet. Additionally, they suggest that all

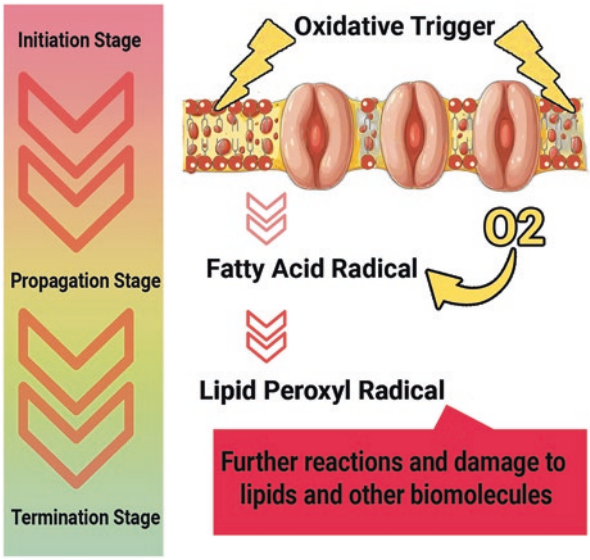

Fig. 5.2 The process of membrane lipid peroxidation

individuals with psychiatric illnesses may benefit from a dietary shift toward a diet that excludes refined carbohydrate products.

Polyunsaturated fatty acids (PUFAs) in the neuronal membrane are vulnerable to peroxidation mediated by reactive oxygen species. The process of membrane lipid peroxidation (Fig. 5.2) includes three stages: initiation, propagation, and termination. In the initiation stage, a reactive oxygen metabolite attacks a methylene group in the lipid, resulting in the formation of a fatty acid radical. During the propagation stage, a reaction between the fatty acid radical and oxygen results in the formation of a lipid peroxyl radical. This radical can further react and cause damage to lipids and other biomolecules.

Dietary interventions targeting oxidative stress, such as fatty acid supplementation and dietary changes, may have potential therapeutic benefits for individuals with these disorders. A diet high in antioxidants, found in fruits, vegetables, and nuts, can help counteract the effects of oxidative stress.

5.5 Nutrient Deficiencies and Mental Illness

The intersection between diet and mental well-being underscores the importance of understanding the role that essential nutrients play in maintaining optimal cognitive function and emotional balance. The complex relationship between nutrient deficiencies and mental illness is evident and supports the notion that the body's nutritional status can significantly impact various aspects of mental health, from mood

regulation to the manifestation of psychiatric disorders. The following table, adapted from Raymond and Morrow (2022), summarizes some of the connections between inadequate nutrient intake and the intricate mechanisms underlying mental health challenges, shedding light on potential avenues for therapeutic intervention and preventative measures. Nutritional deficiencies and mental health will be discussed in more detail in Part II 18 of this book.

Deficient nutrient	Mental illness	Disease	Treatment
Protein and calories	Impaired cognitive and intellectual function	Protein-calorie deprivation	Protein foods, adequate calories
B3 Niacin	Memory loss, hallucinations, dementia	Pellagra	Niacin, food, and/or supplement as needed
B1 Thiamin	Amnesia, encephalopathy, involuntary eye movements, impaired movement	Wernicke-Korsakoff syndrome	Eliminate alcohol; thiamin food or supplement, adequate hydration
Zinc	Taste and smell loss, hallucinations, depression, brain defects during pregnancy	Zinc deficiency	Zinc in food/supplements
B6 Pyridoxine	Abnormal touch sensations, mania, convulsions, abnormalEEG readings	B6 deficiency	Pyridoxine, food, and/or supplement as needed. Eliminate alcohol
B9 Folic acid	Peripheral nerve problems, memory disorder, convulsions; neural tube defects	B9 deficiency	Folate in food and supplements/folic acid in supplements
Iodine	Stunted physical and mental growth	Cretinism	Seafood, fortified salt, supplement
Excessive copper	Mental and movement problems; genetic disorder	Wilson's disease	Low copper diet, including supplements

5.6 Food Sensitivities and Mental Illness

Food sensitivity is still under-recognized as a contributing factor to mental illness. Recent literature review shows evidence and potential pathological mechanisms related to these immune conditions (Fig. 5.3). For instance, Jackson et al. (2012a) and Teitelbaum et al. (2011) have studied schizophrenia and autism, respectively, and associated them with food sensitivities.

The connection between celiac disease (CD) and neurological as well as psychiatric issues has been observed for more than four decades (Bender 1953; Dohan 1966). Celiac disease (CD) is triggered by gluten as an immune-mediated reaction. Gluten is a protein found in wheat, barley, and rye. It presents mainly with gastrointestinal manifestations, and its prevalence is approximately 1% of the population. Recent studies and in-depth understanding of immune response and pathological findings led to the development of gluten sensitivity (GS) as a distinct condition from celiac disease. The prevalence of gluten sensitivity (GS) is estimated to be six

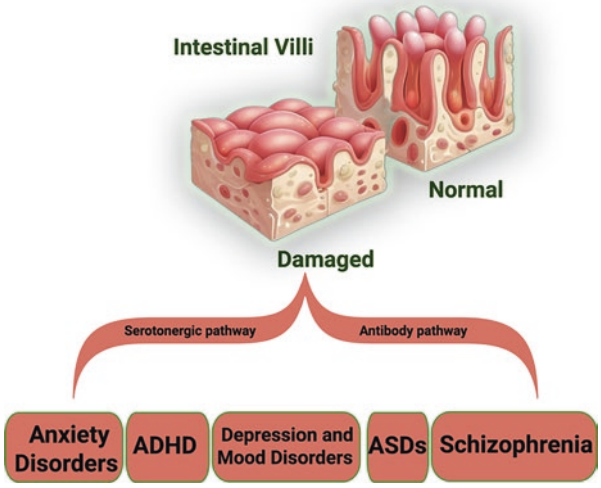

Fig. 5.3 Psychiatric manifestations related to celiac disease and gluten sensitivity. *ADHD* attention deficit hyperactivity disorder, *ASDs* Autism spectrum disorders

times higher than celiac disease (CD). Gluten sensitivity (GS) patients do not exhibit celiac disease (CD) antibodies or villous atrophy. Instead, their gliadin antibodies testing may be positive.

Patients with gluten sensitivity (GS) also experience various neurological and psychiatric complications. It is noteworthy that, despite the absence of gut-related symptoms, neurological and psychiatric disorders in gluten sensitivity (GS) patients may be the main manifestations of the disease, leading to potential underrecognition and lack of treatment.

Immune responses that are gluten-mediated can result in a range of neurological and psychiatric disorders. Studies indicate that as many as 22% of celiac disease patients develop psychiatric or neurological disorders (Briani et al. 2008), and up to 57% of individuals with unexplained neurological disorders are positive for antigliadin antibodies (Hadjivassiliou et al. 1998).

CD and GS have been linked to a diverse array of psychiatric symptoms and disorders. The most frequently reported ones include anxiety disorders (Addolorato 2001), depressive and mood disorders (Cicarelli et al. 2003; Carta et al. 2002), attention deficit hyperactivity disorder (ADHD) (Niederhofer and Pittschieler 2006), autism spectrum disorders (Genuis and Bouchard 2010), and schizophrenia (Bender 1953; De Santis et al. 1997; Samaroo et al. 2010; Cascella et al. 2011). Although research on the association between most psychiatric disorders and GS and CD is limited, there is growing evidence pointing to various connections.

5.6.1 Anxiety Disorders

Various forms of anxiety have been linked to gluten intolerance. In one study, CD patients were shown to exhibit a significantly greater likelihood of experiencing state anxiety compared to control subjects. Interestingly, after following a gluten-free dietary shift for 1 year, symptoms related to the state of anxiety were notably improved (Addolorato 2001). Gluten response has also been associated with panic disorder, and social phobia, among other anxiety disorders. Notably, Addolorato et al. (2008) pointed out a significant high occurrence of social phobia among CD patients compared to normal controls. Moreover, higher lifetime prevalence of panic disorder was found in CD patients (Carta et al. 2002), and the relation between CD and anxiety has also been confirmed by Häuser et al. (2010).

5.6.2 Attention Deficit Hyperactivity Disorder (ADHD)

Several studies have indicated a potential relationship between celiac disease (CD) and attention deficit hyperactivity disorder (ADHD). One study assessed CD patients with ADHD symptoms, and observed an "overrepresentation" of these symptoms in untreated CD individuals. The study reported that a 6-month gluten-free dietary modification led to an improvement in ADHD symptoms, with a majority of patients (74%) expressing a strong tendency to follow that gluten-free diet to keep the significant relief of their symptoms (Niederhofer and Pittschieler 2006).

5.6.3 Depression and Mood Disorders

Associations between gluten sensitivity, celiac disease, and depression along with related mood disorders have been reported. Carta et al. (2002) found that major depressive disorder, adjustment disorders, and dysthymic disorder were more prevalent in patients with CD in comparison to control subjects. Subsequent research by Cicarelli et al. (2003) further supported an increased occurrence of dysthymia in CD individuals compared to controls. Another study by Ludvigsson et al. (2007) indicated that CD patients were more likely to receive a diagnosis of subsequent depression, when compared to non-CD individuals. In a study by Ruuskanen et al. (2010), an elderly gluten-sensitive population had double-fold increased likelihood of experiencing depression compared to an elderly non-gluten-sensitive group. Additionally, Corvaglia et al. (1999) noted a reduction in depressive manifestations following adherence to a gluten-free dietary approach.

5.6.4 Autism Spectrum Disorders

Numerous studies have established a relationship between gluten intolerance and autism spectrum disorders (ASD). Research on the connection between ASD and autoimmune diseases, particularly celiac disease (CD), has shown significant findings. Atladottir et al. (2009) reported an elevated ASDs risk in children whose mothers have a history of celiac disease and rheumatoid arthritis. Another study involving ASDs children demonstrated a high prevalence of family members with diseases like rheumatoid arthritis and irritable bowel syndrome (Valicenti-McDermott et al. 2008). Also, abnormalities in intestinal permeability were more prevalent in ASDs individuals and their family members, compared to controls. De Magistris et al. (2010) showed that improved intestinal permeability occurred in individuals with ASDs who followed a gluten- and casein-free dietary approach. Additional studies on gluten- and casein-free dietary approaches have yielded desired outcomes for ASD patients (Knivsberg et al. 2002; Whiteley et al. 2010; Hsu et al. 2009). In a different study, some autistic patients were found to produce antibodies targeting both gliadin peptides and Purkinje cells (Vojdani et al. 2004). These interactions may be linked to the onset or worsening of ASD symptoms. Notably, it is unclear if the exclusion of casein exerted any positive effects on its own, as much of the research in this domain revolves around gluten- and casein-free dietary approaches.

5.6.5 Schizophrenia

Schizophrenia appears to have a particularly strong association with gluten sensitivity (Kalaydjian et al. 2006), dating back in history to as early as 1953 when Bender observed a propensity for schizophrenic children to have celiac disease. Graff and Handford (1961) presented a case study in 1961 where five schizophrenia with celiac disease patients were admitted to the same hospital within a year. Dohan conducted several studies on schizophrenia and gluten, beginning in 1966, revealing lower schizophrenia prevalence in areas where grain is less consumed. His studies also demonstrated improved schizophrenic symptoms on a milk- and cereal-free diet (Dohan et al. 1969). Other studies by Dohan showed faster discharges for patients on the diet (Dohan and Grasberger 1973) and disruptions in recovery when gluten was reintroduced to a previously gluten-free diet (Singh and Kay 1976). In another study, rats injected with fractions of gliadin polypeptides exhibited reactions such as seizures and unusual behaviors, suggesting a potential link to schizophrenia's pathogenesis (Dohan et al. 1978).

A 1997 case study described a woman initially diagnosed with schizophrenia based on symptoms like hallucinations and avolition. After admission for psychiatric symptoms, she was diagnosed with celiac disease and showed remarkable improvement on a gluten-free diet. EEG and SPECT scan results normalized, and she discontinued antipsychotics, remaining symptom-free at a 1-year follow-up (De

Santis et al. 1997). Singh and Kay's trial on a locked research ward reported significant improvement on psychopathology measures and social participation during a gluten-free phase, with regression upon gluten challenge (Singh and Kay 1976). Rice et al. also showed improvements in gluten-free dietary approach (Rice et al. 1978). Vlissides et al.'s double-blind trial showed changes under gluten-free diets (Vlissides et al. 1986). Negative studies may be due to differences in the selection criteria of patients with gluten sensitivity (Potkin et al. 1981).

Cascella et al. (2011) reported a significantly higher prevalence of anti-gliadin antibodies in schizophrenia patients, from blood samples of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study. Another study found increased gliadin antibody levels in schizophrenia patients, indicating a potential correlation (Dickerson et al. 2010). A separate study replicated this finding, reporting a higher percentage of schizophrenia patients with anti-gliadin antibodies when comparing them to controls (Jin et al. 2012). Reichelt and Landmark showed that specific IgA antibody is much increased in the schizophrenia group than in controls (Reichelt and Landmark 1995).

Samaroo et al. (2010) suggested that the immune response may be different in schizophrenia patients than from autoimmune-driven CD, providing further evidence for the distinct nature of gluten sensitivity.

5.6.6 Food Sensitivities Implicated Pathway in Mental Illness

It is postulated that an "antibody" or a "serotonergic" cause, or both, may play a role in the psychiatric complications. Antigliadin antibodies (AGAs) are IgA and IgG antibodies in the sera of celiac disease patients (Jackson et al. 2012b).

In the central and peripheral nervous system neurons, a phosphoprotein named "synapsin I" is present, which has a crucial role in the formation and maintenance of synaptic vesicles. Cross-reactivity between anti-gliadin antibodies and synapsin I has been studied by Alaedini et al. (2007), revealing that some patients with gluten sensitivity (GS) showed either IgG or IgA antibodies to synapsin I, suggesting a potential mechanism for neurological dysfunction.

Earlier research has indicated that, in monocytes and macrophages, gliadin possesses the ability to trigger cytokine production (Palová-Jelínková et al. 2005). Thomas et al. (2006) exposed peritoneal macrophages of rodents to various concentrations of gliadin, which resulted in the activation of pro-inflammatory genes. Ashkenazi et al. demonstrated a comparable response of lymphocytes in both schizophrenic patients and CD patients when stimulated with gluten (Ashkenazi et al. 1980; Pavol et al. 1995; Denicoff et al. 1987).

Recently, anti-ganglioside antibodies and anti-glutamic acid decarboxylase (anti-GAD) antibodies have been associated with gluten sensitivity (GS) and neurological complications. Glutamic acid decarboxylase plays a role in producing gamma-aminobutyric acid (GABA), a vital inhibitory neurotransmitter. More than half of patients with gluten ataxia (GA) were found to have high concentrations of

anti-GAD antibodies in Purkinje cells and peripheral nerves. In cases of both neurological issues and diagnosed celiac disease (CD), the prevalence of these antibodies can be as high as 96%, suggesting a potential predisposition to neurological problems in patients with enteropathy (Hadjivassiliou et al. 2004; Williamson et al. 1995).

Hadjivassiliou et al. (2008) showed that in CD patients, 55% reacted positively to more than one type of tissue transglutaminase TG. This study also pointed out the accumulation of TG2 and IgA deposits in the blood vessels of the brain, potentially triggering an immune reaction to the exposed brain cells. In another study, the cerebellum, medulla, and pons also had IgA deposits (Hadjivassiliou et al. 2006).

For the "serotonergic" hypothesis, one research study revealed depressive and behavioral symptoms, accompanied by low levels of free tryptophan, in the majority of celiac disease (CD) adolescents prior to their CD diagnosis. The study further revealed that following a gluten-free dietary approach resulted in better outcomes related to depressive symptoms and behavioral issues improvement, with a rise in free L-tryptophan levels (Pynnönen et al. 2005). Additionally, a gluten-free dietary approach for 1 year resulted in a significant rise in concentrations of major metabolites of serotonin and dopamine (Hallert and Sedvall 1983). While this hypothesis remains incomplete, it suggests a potential involvement of L-tryptophan and serotonin in the pathophysiological connection between gluten-mediated immune responses and psychiatric comorbidities.

5.7 Disrupted Energy Metabolism and Mental Illness

Abnormalities related to brain energy metabolism have been linked to bipolar disorder (Nierenberg et al. 2013). Bipolar disorder (known previously as manic depression or manic-depressive illness) is a chronic mental illness that causes unusual recurrent episodes of depression and mania, with unusual shifts in concentration and activity levels. Despite available treatments, many bipolar patients experience relapses within a year of their previous mood episode (Judd et al. 2008).

Mitochondria are the cell organelles responsible for generating most of the energy to power cell functions. Figure 5.4 highlights the pathogenesis of mitochondrial dysfunction.

Clay et al. in 2011 highlighted some evidences that strongly suggest that bipolar disorder is closely linked to both mitochondrial dysfunction and oxidative stress. Cataldo et al. (2010) have identified structural and functional abnormalities in the mitochondria of the brain and peripheral cells from bipolar disorder individuals. It was noted that the extent of mitochondrial dysfunction was substantial enough to result in neurological and/or psychiatric symptoms, but does not always reach the triggering level of a systemic disease. This is particularly noteworthy considering the substantial energy demands of the brain, which surpass those of any other organ in the body, as emphasized by Peters et al. (2004).

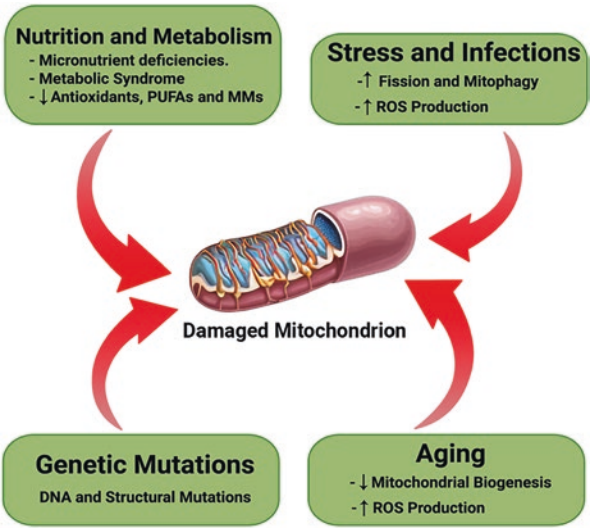

Fig. 5.4 Pathogenesis of mitochondrial dysfunction. *ROS* reactive oxygen species, *PUFAs* polyunsaturated fatty acids, *MM* mitochondrial modulators

Multiple scientific pathways supported the role of "Mitochondrial Dysfunction" in bipolar disorder, including: lower brain energy metabolism due to decreased ATP production and switching to anaerobic glycolysis (Cui et al. 2007; Frey et al. 2007; Naydenov et al. 2007; Stork and Renshaw 2005), upregulation of apoptosis genes (Benes et al. 2006), proteasome degradation, decreased antioxidant defenses and downregulation of mitochondrial genes regulating OXPHOS (Konradi et al. 2004), and increased oxidative stress resulting in higher rate of lipid peroxidation and alterations in calcium levels and metabolism (Kato 2008; Munakata et al. 2004).

From a therapeutic point of view, Nierenberg et al. (2013) have investigated several potential mitochondrial modulators (MMs) as treatment options for bipolar disorder. These MMs included *N*-acetyl-cysteine (NAC), coenzyme Q10 (CoQ10), melatonin, acetyl-L-carnitine (ALCAR), alpha-lipoic acid (ALA), *S*-adenosylmethionine (SAMe), and creatine monohydrate (CM). These substances are already available as dietary supplements or nutraceuticals and have shown tolerability in previous studies.

5.8 Neurotransmitter Precursors Pathway and Mental Illness

Neurotransmitter levels can be much influenced by their dietary precursor's availability. Fluctuating level of these neurotransmitters will have further impacts on the neurological and psychiatric aspects of the individual, being responsible for communicating signals between neurons. Mood regulator neurotransmitters have been implicated in the pathway and management of mental illness. The presence and

significance of neurotransmitters, including acetylcholine (ACh), serotonin (5-HT), glutamate, dopamine, γ-aminobutyric acid (GABA), and histamine, in various food sources have been investigated by Briguglio et al. (2018). Diet can affect neurotransmitter pathways by providing the necessary precursors for their synthesis.

For example, amino acid "Tryptophan" which is obtained from protein-rich foods is a precursor for serotonin (5-HT) synthesis. Reuter et al. (2021) highlighted good supply of tryptophan form dietary sources is associated with a decreased risk of depression. 5-HT, involved in mood regulation, is found in bananas, pineapples, tomatoes, and walnuts.

Similarly, amino acid "Tyrosine" which is also obtained from protein-rich dietary components is a precursor for dopamine synthesis. Studies have shown improvements in cognitive functioning after tyrosine administration (van de Rest et al. 2013). Dopamine, known for its role in reward and motivation, is present in foods like beef, chicken, fish, and bananas.

Acetylcholine deficiency in the brain may cause difficulty in recalling memories, delusions, and confusion. Acetylcholine (Ach) is present in more than 50 plant species, including economically important families such as Gramineae, Leguminosae, and Solanaceae. Various plant extracts and foods like squash, aubergine, spinach, and pea were found to contain significant amounts of ACh.

High protein dietary components also secure a good supply of "glutamate," such as meats, seafood, stews, and soups. Glutamate serves as the brain's most important excitatory neurotransmitter. Additionally, glutamic acid, the precursor of glutamate, is found in seaweeds, fermented beans, cheeses, and tomatoes.

Gamma-aminobutyric acid (GABA) serves as the primary neurotransmitter responsible for facilitating inhibitory synaptic currents through its binding to receptors situated in either the pre- or postsynaptic membranes. Its role involves suppressing nerve transmission in the brain, contributing to the calming of nervous activity. GABA is found in fermented foods like kimchi, yogurt, and sauerkraut.

5.9 Conclusion

In conclusion, diet can affect various pathways in the body that are implicated in mental illness, including the gut microbiome, inflammation, oxidative stress, and neurotransmitter pathways. A dietary approach that emphasizes higher proportion of fruits, fibers, whole grains, and vegetables can promote a healthy gut microbiome, reduce inflammation, and provide antioxidants, which can improve mental health outcomes. In contrast, increased intake of sugar, gluten-rich foods, and processed foods can lead to an unhealthy gut microbiome, increased inflammation, adverse immune reactions and oxidative stress, which can increase the risk of mental illness. These findings are revolutionary and significantly affect the therapeutic approach and clinical outcomes in the prevention and treatment of mental illness. And still many iterations and research work are needed to reach the optimal dietary strategies for promoting mental health. Additionally, research could focus on

identifying specific dietary components or patterns that are most strongly associated with improved mental health outcomes.

In conclusion, the evidence reviewed in this chapter suggests that diet affects the development and management of mental illness in multiple pathways. A dietary approach that promotes a healthy gut microbiome, reduces inflammation and oxidative stress, and provides the necessary precursors for neurotransmitter synthesis could promote mental health and update the clinical practice.

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Chapter 6
Nutrition, the Immune and Inflammatory Systems, and Mental Illness: What Is the Interplay?

Maria Hadjikyriakou, Federika Garcia, Lujain Alhajji, Vanessa Padilla, and Samer El Hayek

Abstract The burgeoning field of Nutritional Psychiatry is based on the interplay between nutrition, inflammation and the immune system, and mental illness. With the discovery of the gut-brain axis as a key mediator between the immune system and inflammation, it has become apparent that nutrition and dietary choices can have a major impact on immune and inflammatory responses in the body, in turn affecting physical health. Emerging research has found that both over- and under-activation of the body's immune and inflammatory responses can contribute to neuropsychiatric disorders. This has thus inspired research into dietary and nutritional interventions for addressing mental illness. While higher quality evidence is still needed, current research into the role of nutritional and dietary interventions as modifiable targets in this network between the immune system, inflammation, and mental illness appears to show promise.

Keywords Nutrition · Mental health · Inflammation · Immune system · Gut-brain axis · Diet · Nutritional psychiatry

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6.1 Introduction

In the 1960s, the term "*psychoneuroimmunology*" was coined to describe the bidirectional connection between the central nervous system and the immune system. The brain can affect the immune system, with chronic psychological stress dampening various immune functions. Conversely, chronic systemic inflammation, whether mild or severe, can interfere with brain functioning, resulting in a range of symptoms from fatigue to overt psychiatric illness (Straub and Cutolo 2018). Changes in the immune system can lead to profound alterations in psychological states, impacting mood and behavior. In this respect, accumulating evidence has described the involvement of the immune system in psychiatric disorders (Rhie et al. 2020).

Elevated levels of peripheral and central inflammatory mediators have been associated with both the onset and progressive course of various neuropsychiatric disorders (Rhie et al. 2020). Hence, inflammatory regulation plays a pivotal role in the pathophysiology of serious mental illnesses (SMI), as well as in the response to therapeutic interventions. When referring to SMI in this chapter, the authors are primarily referring to persons living with diagnosed major depressive disorder, bipolar disorder, anxiety disorders, or schizophrenia.

The levels of inflammatory markers increase when individuals adhere to a diet high in refined starches, sugar, saturated fats, and trans-fatty acids. Alternatively, reduced inflammation is associated with diets abundant in natural antioxidants and fibers from fruits, vegetables, and whole grains (Giugliano et al. 2006). Healthy dietary patterns, such as the Mediterranean diet, have been associated with better mental health compared to "unhealthy" eating patterns, such as the Western diet (Firth et al. 2020).

Dietary habits thus can exert a significant influence on the physical and mental well-being of individuals with SMI through a complex network of physiological mechanisms. Research exploring the potential processes underlying the relationship between diet and mental health has primarily focused on inflammation, oxidative stress, and neuroplasticity. The gut microbiome has emerged as an integral mediator for each of these processes (Berk et al. 2013; Moylan et al. 2014; Jacka et al. 2015; Slyepchenko et al. 2017). A nascent understanding of these pathways has stimulated research into the adjunctive use of nutritional supplements and dietary interventions to target these processes as means of managing common and severe psychiatric disorders. The field of Nutritional Psychiatry has thus emerged as a new frontier in mental health treatment.

This chapter provides a comprehensive overview of this topic, including a thorough examination of the gut-brain axis; the intricate interconnections between nutrition, inflammation, and the immune system; the role of inflammation and the immune system in mental health; and the relationship between micronutrient deficiencies and different SMIs.

6.2 The Gut-Brain Axis

In the time of ancient Greek philosophers, theories involving the connection between the brain and the digestive system were already in existence. By the 1880s, the James-Lange theory of emotion posited a relationship between emotions and the functioning of internal organs through a connection with the brain. The discovery that the enteric nervous system (ENS) derives from precursor cells in the neural crest before differentiating in the gut made it clear that there must be a relationship between the nervous and digestive systems (Mayer 2011).

Coined "The Second Brain" by Dr. Michael Gershon (Gershon 1999), the ENS is now understood to comprise an extensive network of nerve fibers between layers of intestinal muscle and mucosa in the gut with close proximity to major factors of the immune system, including the intestinal-associated lymphoid tissue (GALT) and the mucosa-associated lymphoid tissue (MALT) (Góralczyk-Bińkowska et al. 2022). A bidirectional connection between the ENS and the brain exists, involving vagal nerve fibers as part of the parasympathetic nervous system and sympathetic nerve fibers. However, communication from the gut does not solely occur via neurotransmitters and neuronal signals (Mayer et al. 2022).

The gut microbiome, which consists of all the digestive tract-associated microorganisms, or microbiota, also plays a role in communication with the brain. Microbiota in the gut mainly consists of bacteria that are obligate anaerobes. These bacteria are primarily from two families, or phyla, the Bacteroidetes and the Firmicutes. Over 1000 different bacteria families or phylotypes may be involved with even greater diversity at the species level of bacteria. While bacteria may be the better-studied portion of the gut microbiota, the microbiome may also include other microorganisms such as viruses, yeasts, and parasites. However, the role of such microorganisms in the gut still needs to be further investigated (Bull and Plummer 2014).

The colonization of the gut by microbiota begins at birth, as the newborn is exposed to microbiota in the birthing parent's vaginal canal. It has also been shown that maternal diet and stress during pregnancy affects an infant's microbiome (Chu et al. 2016). As an infant transitions from breastfeeding or formula feeding to solid food, the diversity of the infant's gut microbiota begins to change, further influenced by other environmental factors (Bull and Plummer 2014). Ultimately, the gut microbiota grows to include an estimated 10^{13}–10^{14} microbial cells (Kho and Lal 2018).

The role of the gut microbiome was largely unknown until recent technological advances in gene sequencing technologies. Such advancements have allowed the completion of wide-scale projects, like the Human Microbiome Project, which has begun to elucidate the complexity underlying the function and role of the gut microbiome in metabolism, immunity, and other medical conditions (Kho and Lal 2018).

It is now believed that the gut microbiota can communicate with the brain via three main categories of signaling molecules—immune-based, neuroendocrine-based, and diet-derived metabolites. Membranes of the various gut microbiota can interact with immune cells located in the gut or travel via systemic circulation to

activate other immune-mediated signaling cascades. Other body-derived inputs, including hormones and primary bile acids, can be transformed by gut microbiota into microbial signals. In addition, diet-derived inputs, like amino acids, and breakdown products, like polysaccharides and polyphenols, can be transformed by gut microbiota into microbial signals, which include neurotransmitters and short-chain fatty acids. These then can activate immune-mediated sensors. Microbial signals can travel to the brain via systemic circulation or trigger communication by interacting with other gut-based cells that initiate signaling cascades through the vagal and sympathetic nerve fibers (Mayer et al. 2022).

The brain, in turn, can modulate the activity of the ENS and the gut microbiota via the hypothalamic-pituitary-adrenal (HPA) axis, sympathetic and parasympathetic nerves of the autonomic nervous system (ANS), and immune signaling channels. The central nervous system also influences the composition of the gut microbiome via stress-mediated changes in microbiota gene expression and through ANS control of the gut environment (Margolis et al. 2021).

Other factors and modulators of this complex communication system include the intestinal barrier, which can affect the communication between gut microbiota and inner immune cells depending on various stressors. The blood-brain barrier, which can change its permeability to gut microbiota signals depending on certain stressors, may be another important component of the gut-brain relationship (Mayer et al. 2022).

Emerging research highlights the various pathways in this immensely complex and much more-to-be-discovered gut-brain axis, the degree of complexity of which has earned the label of "connectome." The gut-brain connectome requires a delicate balance of homeostasis, alterations of which likely have a role in various illnesses, including changes in cognitive development (Carlson et al. 2018). The role of the gut-brain axis in nutrition and mental health is discussed in the following sections.

6.3 The Role of Nutrition in Inflammation and the Immune System

Inflammation, as modulated by the immune system, is a means by which the body protects itself against physical, psychological, and environmental stressors. Such stressors include smoking, binge drinking, obesity, lack of sleep, and a poor diet (Berk et al. 2013). An inflammatory response consists of inflammatory inducers, known as pathogen- or damage-associated molecular patterns (PAMPs or DAMPs, respectively); receptors detecting the inducers (i.e., receptors expressed by immune cells such as macrophages or dendritic cells); inflammatory mediators that are induced by the sensors (e.g., cytokines, chemokines, prostaglandins, tumor necrosis factor, interleukin (-1, interleukin-6, and reactive oxygen species); and target tissues that are affected by the inflammation (Bauer and Teixeira 2019).

The concept of "dietary inflammation" can be used to categorize foods or dietary patterns that increase inflammatory markers in the body (Marx et al. 2021). The

Standard American Diet (SAD), which is prevalent in Western societies, is notorious for its calorie-dense foods; high content of ultra-processed foods; and a lack of beneficial omega-3-rich fats, vitamins, minerals, antioxidants, and fiber-rich foods. Such dietary patterns have been associated with negative impacts on immune function as well as increased susceptibility to diseases (Kurowska et al. 2023). This may be due to their notorious effects of triggering oxidative stress and inflammatory pathways, which can significantly affect brain function (Bauer and Teixeira 2019). This phenomenon is evidenced by increased levels of inflammatory markers and cytokines, such as C-reactive protein (CRP), interleukin (IL)-6, tumor necrosis factor (TNF)-a, IL-1β, IL-12, along with markers of metabolic syndrome and other disease states (Estrada and Contreras 2019).

In contrast, foods that support anti-inflammatory pathways, such as omega-3-rich foods, micronutrients, fiber, prebiotics, and probiotics, have been recognized for their beneficial impacts on health and well-being. Mediterranean-style diets have consistently demonstrated efficacy in improving inflammatory markers and preventing and treating various disorders, including those related to brain and cognitive function.

Nutrition and dietary choices also affect the diversity and quality of the gut microbiome, which in turn impacts immune function and systemic inflammatory processes (Estrada and Contreras 2019). Overly restrictive diets that are often adopted for rapid weight loss, such as ketogenic, low-carbohydrate, and paleo-diets, can have detrimental effects on gut microbiota diversity and quality due to a lack of fiber-rich foods. These diets and their effects on the gut microbiome ultimately heighten the likelihood of triggering the inflammatory cascade pathways in the body, impacting the susceptibility to stress and health-related issues, including neuroinflammation in the brain (Horn et al. 2022). A Western or SAD diet, with its high saturated fats, sugars, red meats, and salt content in addition to low omega-3-rich fish, polyphenols, and fiber-rich foods, negatively impacts the gut microbiome. On the contrary, individuals adhering to a Mediterranean diet often show increased beneficial gut microbial diversity, which is inversely associated with inflammatory markers (Merra et al. 2020).

Short-chain fatty acids (e.g., butyrate) play a vital role in this context and are produced by gut bacteria as they ferment dietary fibers. Short-chain fatty acids not only provide energy for colonocytes but also exhibit anti-inflammatory and anti-carcinogenic benefits (Merra et al. 2020). Thus, a plant-based diet rich in polyphenols and fiber from fruits, vegetables, nuts, seeds, whole grains, and fermented foods is crucial. Such a diet fuels microbial diversity and richness, which is essential for maintaining a healthy gut-brain axis. In addition, fermented foods serve as a substrate for gut bacteria growth, further facilitating this type of diet's beneficial effects on health (Bell et al. 2018). These foods, rich in probiotics, also contribute to gut microbiome health by promoting the growth of beneficial gut bacteria and the production of mood-regulating neurotransmitters (Tripathi et al. 2023).

The connection between the gut and brain, as mediated by dietary choices, emphasizes the importance of a healthy, nutrient-dense, and anti-inflammatory diet as a crucial pillar in optimizing health and immune function. The abundance and diversity of gut microbiota, which is significantly influenced by our dietary patterns,

underscore the profound impact of nutrition on our overall well-being as achieved by prioritizing dietary choices and opting for a plant-focused diet rich in fermented foods.

6.4 The Intersection of Inflammation, the Immune System, Nutrition, and Mental Health

Both over- and under-activation of the immune inflammatory response can trigger illness and disease, including cardiovascular disease (Lopez-Candales et al. 2017), cancer (Korniluk et al. 2017), and neuropsychiatric disorders (Yuan et al. 2019). Inflammation has been implicated in multiple psychiatric disorders, including post-traumatic stress disorder (PTSD), major depressive disorder (MDD), bipolar disorder (BD), and schizophrenia. Inflammation-related factors (IRFs) may have the potential to act as biomarkers for psychiatric disorders, which may allow for future clinical applications such as providing accurate diagnoses, staging of illnesses, and monitoring treatment responses. The relationship between psychiatric disorders and the systems that regulate inflammation still remains poorly understood and requires further study, including investigation of genetic and epigenetic factors. In addition, the inflammation process may differ based on where it occurs; for example, inflammation effects at the blood-brain barrier may differ from inflammation effects in the periphery (Sonar and Lal 2018).

Longitudinal studies examining IRFs and psychiatric disorders are necessary as IRFs can fluctuate and vary depending on multiple factors. A study examining meta-analyses of inflammation-related factors and psychiatric disorders found that among inflammatory factors, IL-2 is significantly low in suicide; IL-4 is significantly low in suicide but high in BD; sIL-6R is significantly high in BD; and sIL-2R is unchanged in PTSD. It also found that IL-6 and CRP are the two most commonly increased IRFs in MDD, suicide, sleep disorders, and schizophrenia, while nerve growth factor (NGF) is most commonly decreased in MDD and schizophrenia. Meta-analyses of related biomarkers showed consistent changes in IL-6 across varying stages of schizophrenia, including higher levels in persons who are acutely ill, chronically ill, and with their first-episode schizophrenia than in controls. CRP is the only IRF that was reported to change in all three BD (manic, depressive, and euthymic) states (Yuan et al. 2019). Studies have also shown that patients with MDD and schizophrenia have a higher degree of oxidative stress markers (Moylan et al. 2014; Nemani et al. 2015).

In humans, a reduction of microbiota richness and diversity has been implicated in patients with depression (Marx et al. 2017). This can result from dietary patterns that are calorically dense but nutrient-poor, such as those discussed previously, with high intakes of sugar, fat, processed foods, and alcohol, contributing to chronic low-grade inflammation (Bauer and Teixeira 2019). Increased gut permeability through its epithelial barrier may also be implicated in depression by increasing

bacteria-derived lipopolysaccharides and leading to increased activation of the immune response systemically, including the production of inflammatory cytokines and activation of nitro-oxidative stress pathways.

Research focusing on nutrition and mental health has mainly focused on biological pathways, such as inflammation, oxidative stress, neuroplasticity, and the gut microbiome (Berk et al. 2013), with many studies focusing on diet and nutritional interventions that can affect these pathways. However, given the bidirectional relationship between the brain and the gut, mounting evidence, mainly from animal studies, suggests that gut microbiota can also affect mental health through multiple neuroimmunological pathways, including brain-derived neurotrophic factor (BDNF), serotonin neurotransmission, the HPA axis, and general immune function (Kelly et al. 2016).

Born out of the above proposed mechanisms, the field of Nutritional Psychiatry continues to explore dietary and nutrient-based interventions for treating mental illness (Sarris 2019). The role of nutrition in mental illness is further explored in the next section.

6.5 Nutrition, Micronutrients, and Supplements as Interventions for Mental Illness

The brain relies on the availability of lipids, minerals, amino acids, and vitamins to properly develop its structures and function. Nutrients provide energy to the body and the brain while maintaining the integrity of neuronal structures. Specific diseases related to nutritional deficiencies have been found to present with psychiatric signs and symptoms and are corrected by nutritional supplementation, such as pellagra, beriberi, and scurvy (Raju 2017). Nutrients like vitamins B1, B6, B9 (folate), and B12 have become a focus of study for the linkage between nutrients and the risk for or presence of mental health disorders.

The literature on nutrition and mental health emphasizes the role of nutritients on stress, sleep, anxiety, and cognition. A 2021 review highlighted the relationship between the role of nutrients and their effect on specific mental health disorders (Muscaritoli 2021). To protect the brain, preserve cognition, and enhance well-being, individuals may benefit from the modulation of stress and the reduction of inflammation via a balanced diet full of specific micronutrients. Omega-3 polyunsaturated fatty acids (PUFAs), eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), alpha-tocopherol, magnesium, and folic acid are micronutrients that appear to have a beneficial effect on mental health (Muscaritoli 2021). In this section, the authors discuss the relationship between micronutrients and SMI, both from a perspective of prevention or progression of illness, and discuss the role of nutrients as adjuvants to current treatment modalities.

6.5.1 Schizophrenia

Schizophrenia is a chronic mental health condition with a complex pathophysiology involving symptoms such as hallucinations, delusions, blunted affect, alogia, anhedonia, and avolition. Despite the availability of antipsychotic medications that control the exacerbation of symptoms, pharmacotherapeutic agents can fall short of providing complete remission of symptoms for individuals living with schizophrenia. As nutrition possibly plays a role in the pathophysiology of schizophrenia, we explore the current evidence for the role of nutrition in schizophrenia.

In schizophrenia, glutamatergic, dopaminergic, and γ-amino butyric acid-ergic neurotransmitter systems seem to be dysregulated. Moreover, inflammation, oxidative stress, immune dysregulation, and genetics appear to play a role in the pathophysiology of schizophrenia (Deng and Dean 2013). Foods deficient in essential fatty acids or diets leading to autoimmune reactions (e.g., reactions to gluten) have also been linked to the development of schizophrenia. Vitamin D, folic acid, and iron are three specific micronutrients that may be related to an increased risk of schizophrenia (McGrath et al. 2011). Studies of famine, in which mothers experienced severe prenatal deficits of protein, calories, and micronutrients, have highlighted how offspring's brain development can be altered by nutritional deficiencies and associated with an increased risk of developing schizophrenia later in life. Moreover, elevated maternal homocysteine levels during the third trimester of pregnancy have been associated with a greater risk of schizophrenia in offspring. However, epidemiological studies and randomized controlled trials (RCTs) are needed to further establish the effects of any specific micronutrient supplementation during pregnancy on schizophrenia outcomes among offspring.

A 2018 systematic review and meta-analysis on nutritional deficiencies and first-episode psychosis found that low vitamin D and folate deficiency were more common at illness onset and could be associated with worse symptomatology (Firth et al. 2018). Moreover, individuals already living with schizophrenia have been found to have either a deficiency or excess of essential trace elements such as calcium, zinc, selenium, copper, and manganese. This may be partly because these individuals have a higher likelihood of experiencing barriers to a healthy dietary lifestyle. With a higher likelihood of consuming sugars and processed food (usually high in sodium, cholesterol, and saturated fats), individuals with schizophrenia face a greater risk of developing obesity, diabetes mellitus, and metabolic syndrome. These medical comorbidities can in turn increase the risk of cardiovascular disease and immune dysfunction. Individuals with schizophrenia may thus benefit from switching to diets high in fiber, which are associated with high levels of short-chain fatty acids. Adopting a Mediterranean-style diet may also help reduce the negative impact of immune and cardiovascular issues, which have been linked to increased mortality rates in people with schizophrenia (Joseph et al. 2017).

Though not well established, ketogenic diets, which are characterized by high-fat, moderate-protein, and very low–carbohydrate content, may have a potential therapeutic role in schizophrenia. While studies on ketogenic therapy in SMI are

emerging, more randomized controlled trials are needed to establish efficacy and safety (Sarnyai and Palmer 2020) and to clarify proposed mechanisms by which ketosis may alleviate stress and reduce inflammation in neurodegenerative and neuroprogressive disorders (Morris et al. 2020).

The field of Nutritional Psychiatry continues to explore a wide variety of hypotheses behind the pathways for schizophrenia (e.g., micronutrient deficiencies, impairment in glucose metabolism, inflammation, immune dysregulation, and altered gut microbiota). However, the evidence for nutritional interventions in schizophrenia remains limited (Teasdale et al. 2020). Despite the interest in studying and discovering these pathways, research is still needed to develop precision-focused dietary manipulation for schizophrenia prevention. Moreover, how to effectively and holistically manage the daily nutrition of individuals living with schizophrenia remains a challenge (Onaolapo and Onaolapo 2021). Meanwhile, multidisciplinary programs such as "Keeping the Body in Mind" are examples of how mental health providers and other clinicians can work together to provide nutritional interventions and lifestyle modifications to prevent weight gain in individuals during the early stages of schizophrenia (Curtis et al. 2016).

6.5.2 Bipolar Disorder

Bipolar disorder is a severe mood disorder characterized by episodes of mania, hypomania, and depression. Thoughts, behavior, mood, motor activity, sleep pattern, and overall daily functioning are impaired during episodes of illness exacerbation. Individuals living with bipolar disorder may have challenges with impulsivity and difficulty in choosing healthier lifestyles.

Compared to other nutritional supplements and as polyunsaturated fatty acids (PUFAs) comprise more than one-third of brain lipids, omega-3 (*n*-3) PUFAs have been extensively studied in mood disorders. These include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Omega-6 (*n*-6) PUFAs have also been studied in bipolar disorder. In fact, some mood stabilizers may decrease the metabolism of *n*-6 PUFAs, potentially as another means for their efficacy in bipolar disorder. It seems that systematic reviews and meta-analyses have found evidence that in bipolar disorder, depressive symptoms and not manic symptoms may be improved by the adjunctive use of omega-3 fatty acids (Bozzatello et al. 2016). Moreover, a 2020 randomized controlled trial found that DHA supplementation improved cognitive performance in emotion inhibition in individuals with bipolar disorder (Ciappolino et al. 2020). A 2022 randomized controlled study found that a high *n*-3, low *n*-6 PUFA diet was associated with a reduction in mood variability in patients with bipolar disorder over 12 weeks (Saunders et al. 2022). More studies are needed to replicate the findings before widely recommending nutritional supplementation with PUFAs as an adjuvant to the usual management of mood variability in individuals with bipolar disorder.

A 2023 systematic review provided updates on the available evidence behind the relationship between bipolar disorder and fatty acids, micronutrients, and

N-acetylcysteine (NAC) (Gabriel et al. 2023). In addition to maintaining a healthy diet to minimize the increased risk of metabolic problems in individuals with bipolar disorder, specific nutrient supplementation appears to improve symptoms of bipolar disorder. Omega-3, folic acid, and zinc are the micronutrients most commonly found to be helpful, as well as seafood consumption. Other nutrients such as creatine, carnitine, vitamin D, inositol, and NAC have been found to have mixed evidence in the treatment of bipolar disorder. Newer studies are exploring the possible benefit of coenzyme Q10 and probiotics in targeting bipolar disorder symptomatology (Gabriel et al. 2023).

Dietary modifications and nutritional supplementation may be helpful for individuals with bipolar disorder. However, more studies are needed to establish which specific nutritional interventions might be effective as adjunctive treatments.

6.5.3 Depression

Major depressive disorder is a highly prevalent mood disorder and a leading cause of global health-related burden and disability (World Health Organization n.d.). Symptoms of depression include experiencing a persistently low or depressed mood for at least 2 weeks, with associated anhedonia or decreased interest in pleasurable activities, feelings of guilt or worthlessness, lack of energy, poor concentration, appetite changes, psychomotor changes, sleep disturbances, and suicidal thoughts.

Dietary inflammation has been associated with an increased risk of developing major depression. Multiple biological pathways appear to specifically mediate the relationship between depression and nutrition, including inflammation, oxidative stress, epigenetics, mitochondrial dysfunction, the gut microbiota, tryptophan-kynurenine metabolism, the HPA axis, neurogenesis, BDNF, and obesity (Marx et al. 2021). These factors appear to interconnect and overlap. Moreover, as with schizophrenia, specific diets may also indirectly increase depression risk by contributing to the development of chronic comorbid illnesses, such as diabetes, metabolic syndrome, and cardiovascular disease.

Pharmacological interventions, including the use of antidepressants, and lifestyle interventions have been associated with a reduction in inflammation and depressive symptoms. Dietary interventions that help to reduce inflammation have also been found to improve depressive symptoms. The SMILES (Supporting Modification of Lifestyle in Lower Emotional States) study was the first randomized controlled trial to examine an adjunctive dietary intervention in the treatment of moderate to severe depression. In this 12-week trial, 67 participants were assigned to either a dietary support group or social support group. One-third of those in the dietary support group achieved remission of major depression (as measured by the Montgomery and Asberg Depression Rating Scale at baseline and after 12 weeks of intervention), while only 8% of those in the control group achieved remission (Jacka

et al. 2017). Their findings suggest that diet modifications may be an effective and accessible treatment strategy for the management of depression.

Research is ongoing to identify the role of micronutrients in major depression, particularly the role of omega-3 fatty acids. The evidence is mixed for major depression, but some studies have found fatty acids to be effective therapeutic agents to reduce depressive symptoms, particularly for those individuals presenting with greater symptom severity (Bozzatello et al. 2016). Despite findings and growing evidence that fatty acids may improve depressive symptoms, currently, there is no consensus on their use as part of the treatment of depression.

A 2018 systematic literature review found that foods with the highest "antidepressant food score" (AFS), a nutrient profiling system with clinical evidence to support their role in depressive disorders, were oysters, mussels, other seafood, organ meats, leafy greens, lettuces, peppers, and cruciferous vegetables. These foods are characterized by a higher nutrient density of the following 12 nutrients: folate, iron, long-chain omega-3 fatty acids (EPA, DHA), magnesium, potassium, selenium, thiamine, vitamin A, vitamin B6, vitamin B12, vitamin C, and zinc. The study suggests that researchers and clinicians should utilize foods with the highest density of antidepressant nutrients in their investigations to further explore the role of certain foods in the prevention and recovery from depression (LaChance and Ramsey 2018).

Given the widespread use of vitamins and mineral nutritional supplements, a 2020 systematic review of 23 studies explored the role of broad-spectrum micronutrient formulas for the treatment of depression in adults who were not using psychotropic medications. Due to the variability in the nutrients studied, it was not possible to identify the specific benefits of these treatments (Blampied et al. 2020).

Genetic polymorphisms, such as those of the methylenetetrahydrofolate reductase (MTHFR) gene, have been studied in connection with an individual's propensity to experience a major depressive episode (Cho et al. 2017). The Food and Drug Administration (FDA) approved EnLyte in 2011, which is labeled as "medical food," as a folate supplement for patients with MTHFR gene polymorphisms and who are at risk of depression due to the subsequent deficiency of folate and cobalamin. A 2016 randomized controlled trial enrolled 330 depressed individuals with abnormalities of the MTHFR gene to receive either a combination of reduced B vitamins and micronutrients or a placebo. Among those using the supplement, 42% achieved complete remission by week 8 and on average there was a 12-point reduction on the MADRS over the study time, with clinical improvement correlating with a significant reduction in homocysteine levels (Mech and Farah 2016). And so, specific populations, such as those with abnormalities in the MTHFR gene, may benefit from nutritional supplementation when managing depression.

There is growing evidence that probiotics may alleviate depressive symptoms, given their impact on the gut-brain axis and the microbiome. However, the probiotic strain, the dosing, and the duration of treatment have varied widely across studies (Wallace and Milev 2017). To assess the tolerability and efficacy of probiotics as an adjuvant in the treatment of major depression, a randomized controlled study of 50 participants found that those in the probiotic groups had a greater improvement in

depressive symptoms, as measured by the Hamilton Depression Rating Scale-17 (HAM-D) scores and when compared to the placebo group (Nikolova et al. 2023). A more extensive systematic review and meta-analysis of RCTs, involving 776 participants and using the Beck Depression Inventory (BDI) to assess depression, reported a potentially positive therapeutic role of probiotics in alleviating depression (Lin et al. 2023).

Acetyl-L-carnitine has also been found to improve depressive symptoms significantly (Wang et al. 2014). Specific conditions such as end-stage renal disease may lead to an imbalance of L-carnitine homeostasis. In a 2017 study of patients undergoing hemodialysis, low baseline levels of acylcarnitine types correlated with higher depression scores. When L-carnitine supplementation was provided, thus increasing serum levels of acylcarnitine, depression scores improved (Tashiro et al. 2017). Acetyl-L-carnitine appears to impact neuroplasticity, membrane modulation, and neurotransmitter regulation, which highlights a novel mechanism of action to target depressive symptoms. Acetyl-L-carnitine has been found to be well-tolerated. Still, more data is needed to better elucidate its role as either monotherapy or as an adjuvant for the treatment of major depression.

In summary, moderate-quality evidence has already been identified for the beneficial effects of omega-3 polyunsaturated fatty acids, probiotics, and acetyl-L-carnitine supplementations in depression. However, despite promising data on the role of nutrition in depression, the associations between dietary factors and the prevention and treatment of depression have not yielded high-quality evidence (Xu et al. 2021).

6.5.4 Anxiety Disorders

Anxiety disorders are common mental health disorders affecting individuals across the world, with higher prevalence rates among women. Classic symptoms of anxiety involve restlessness, constant worry, panic, and stress out of proportion to the impact of any given event. Anxiety can affect the whole body by increasing the sensation of fatigue or leading to somatic symptoms such as excessive sweating, nausea, headaches, and palpitations. Anxiety can affect the brain by interfering with cognition and concentration or lead to changes in behavioral patterns by exhibiting hypervigilance or irritability.

Compared to other SMI, such as depression, there is less known about the role of nutrition in anxiety disorders. A scoping review of 1541 articles found associations between lower levels of anxiety and a higher intake of fruits and vegetables, omega-3 fatty acids, “healthy” dietary patterns, caloric restriction, breakfast consumption, ketogenic diet, broad-spectrum micronutrient supplementation, zinc, magnesium, selenium, probiotics, and phytochemicals. On the contrary, higher anxiety levels were associated with a high-fat diet, inadequate tryptophan and dietary protein intake, high intake of sugar and refined carbohydrates, and “unhealthy” dietary patterns (Aucoin et al. 2021).

In an attempt to provide recommendations for dietary modification to prevent anxiety and avoid inflammation, a meta-analysis explored the association between a pro-inflammatory diet and anxiety. It found that the risk of anxiety disorders was elevated in the pro-inflammatory diet group (e.g., eating red meat, processed food, and animal oils) compared to the anti-inflammatory diet group (e.g., eating fruit, vegetables, fish, whole grains, and olive oil). The incidence risk was more significant for females than males (Li et al. 2022).

Thus, in addition to offering psychotropic medications and psychotherapy as treatment modalities for anxiety, eating a healthy diet can be one of the multiple strategies to cope with anxiety.

6.6 Conclusion

Terms such as the "gut connectome," "gut-brain axis," "psychoneuroimmunology," and "nutritional psychiatry" exist due to emerging data on the interplay between the gut, the brain, the immune system, and both physical and mental health. We are only beginning to understand this complex relationship and the various proposed mechanisms underlying the crosstalk that ranges from immune-mediated cascades to hormonal signals.

Current evidence showing various diets' impact on inflammatory pathways, the gut-brain axis, the immune system, and their associations with mental health has sparked interest in the investigation of modifiable targets within this network. Unfortunately, research for nutrient-based interventions for mental illness has largely been mixed, often plagued by placebo effects. Research studies investigating dietary interventions are also limited by methodological differences in analyzing a person's diet, further restricted by recall bias and expectancy bias. While there are broad groups of diets that have been associated with mental illness (e.g., pro-inflammatory versus anti-inflammatory diets, natural whole-food diets versus processed foods), more refined studies are needed to better identify specific inflammatory biomarkers and aspects of the gut-brain axis that in turn can help to investigate modifiable nutritional and dietary targets for the treatment of mental illness. In addition, there may not be a "one size fits all" approach to modulating nutrition and diet. And so, more research is needed to investigate individualized approaches and algorithms for modifying diet and nutrition as it may affect mental illness (Sarris 2019; Jacka 2017).

Still, the current evidence supporting the growing field of Nutritional Psychiatry makes for a promising avenue of research within the realm of integrative medicine and amid the increasingly popular focus on wellness and lifestyle changes.

Key Points

- Diet and nutrition affect the immune system and systemic inflammatory processes.
- The gut-brain axis, including the gut microbiome, is an important mediator of the relationship between diet, nutrition, the immune system, inflammation, and mental health.
- Higher quality evidence and further research is needed to recommend specific nutritional interventions for mental illness.

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Part II
Diet-Brain Connection and Nutritional Deficiencies

Chapter 7
The Impact of Gut Microbiota on Mental Health

Mahmoud Tarek Hefnawy, Kholoud Khaled Elsamman, Abdallah Abbas, and Yousef Hawas

Abstract This chapter delves deeply into the intricate relationship between human health and the gut microbiota, with a specific emphasis on the microbiome's impact on mental health. Genetic, nutritional, and environmental variables all have an effect on the gut microbiota, which in turn affects digestion, food absorption, immunological function, and mental health. Dysbiosis, an imbalance in the gut microbiota, has been related to obesity, diabetes, and mental health issues. The gut-brain axis is a communication pathway between the digestive system and the brain that affects emotional and behavioral states as well as immunity and metabolism. Metabolic and mental diseases have potential solutions in a wide variety of therapies. However, a deeper understanding of these complex interactions, individualized strategies, appropriate dosages, and ethical issues is necessary to fully reap the advantages of psychobiotics. This area of study has the potential to increase our knowledge of how diseases develop and lead to new therapies that will benefit people everywhere.

Keywords Gut microbiota · Mental health · Microbiome · Immunity · Psychobiotics

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7.1 Introduction

The gut microbiome consists of the community of microorganisms normally resident in the human gastrointestinal system. There are likely billions of microorganisms in the area. Human health is affected by the gut microbiota, which is influenced by diet, genetics, and the environment (Ling et al. 2022a). The gut microbiota plays a crucial role in vitamin digestion, absorption, and production. It aids in immune system regulation and could have a role in disease prevention. In addition, the gut flora may have an effect on mood and behavior by helping to produce neurotransmitters. For optimal health, it's crucial to keep the gut bacteria under check (Brody 2020). Several factors may change gut flora, including antibiotics, stress, and poor diet. Type 2 diabetes, obesity, and allergic reactions are only some of the disorders that have been associated with changes in gut flora (Hasan and Yang 2019) (Fig. 7.1).

There is a closed loop between the brain and the digestive system. Together, neurons, hormones, and immune cells build this complex web. Many functions, including eating, defending, feeling, and behaving, are controlled by the gut-brain axis (Baothman et al. 2016). The gut microbiota processes several compounds that have an effect on the brain, including neurotransmitters, short-chain fatty acids, and cytokines. These molecules may have an impact on our emotions, behaviors, and cognitive abilities. Adult-onset diabetes and autism spectrum disorder are only two of the many health issues that have been connected to it (Miyoshi and Chang 2017).

Research reveals that disturbances in the gut-brain axis might have far-reaching consequences. More and more research is pointing to a link between one's gut flora

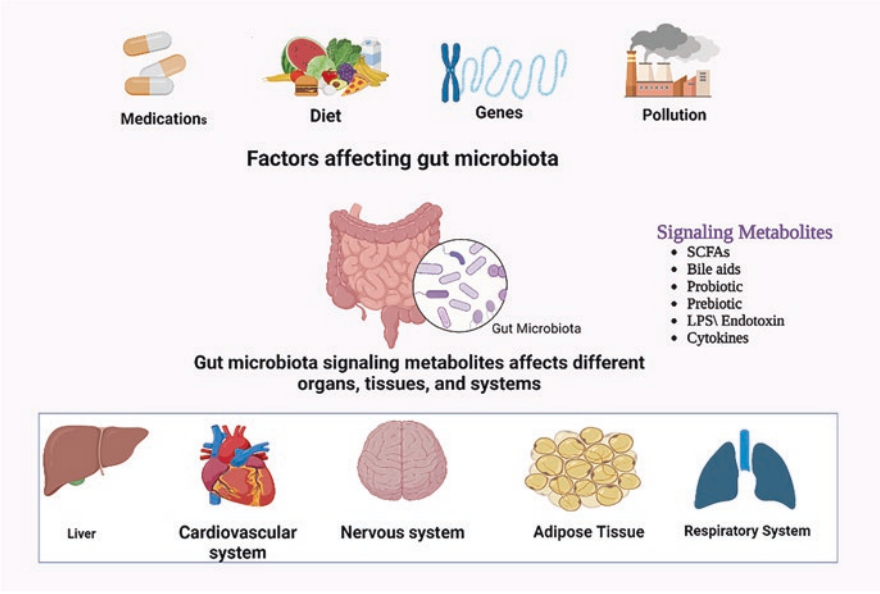

Fig. 7.1 Factors affecting microbiota

and one's mental health. These bacteria are vital to proper digestion and general health and must be protected (Wachsmuth et al. 2022; Chen et al. 2013).

There is emerging evidence that the microbiome in the stomach might affect mental and emotional functioning. Changes in the production of neurotransmitters and other chemicals involved in sending signals throughout the brain, as well as effects on immune system function, are all possible pathways (Chen et al. 2021; Park and Kim 2021).

Anxiety, depression, and autism spectrum disorders have all been related to alterations in gut microbiota, such as a loss of species diversity or an imbalance between beneficial and harmful bacteria (Bhatia et al. 2023). Altering the microbiota in the gut has been shown to affect behavior and cognition in animal studies. Although research has demonstrated a connection between gut microbiota and mental health, the mechanisms behind this relationship remain unclear (Luczynski et al. 2016; Morais et al. 2021). This emerging field of inquiry implies the possibility of developing novel therapeutics for mental health issues by focusing on the microbiome of the digestive tract.

This chapter examines the consequences of the new way of thinking about mental health that has resulted from research on the linkages between the gut microbiota and mental health concerns, including depression and anxiety.

7.2 The Gut-Brain Axis

7.2.1 Definition and Significance

The diverse community of bacteria that lives in a human digestive system is called the gut microbiota or microbiome. The gut microbiota is a population of bacteria, viruses, fungus, and other microorganisms that plays an important role in digestion, absorption of nutrients, and regulation of the immune system, among other functions. The gut microbiota not only helps the body fight off dangerous bacteria and other intruders, but it also has the potential to affect the development and operation of several different organs and systems (Kobayashi et al. 2021) (Fig. 7.2).

Loss of species diversity or an imbalance between good and harmful bacteria are two examples of changes to the gut microbiota that have been shown to be damaging to human health. These shifts have been linked to an increased risk of many illnesses, such as inflammatory bowel disease, obesity, diabetes, and autoimmune disorders (Hur and Lee 2015; Delzenne et al. 2013; Janssen and Kersten 2015; Gálvez-Ontiveros et al. 2020).

Research has shown that changes in gut microbiota composition may be connected to a variety of mental health concerns. Therefore, there has been a rise in interest in the gut-brain axis in recent years. Therefore, there is a rising movement to create cutting-edge therapies that aim to improve people's health and happiness

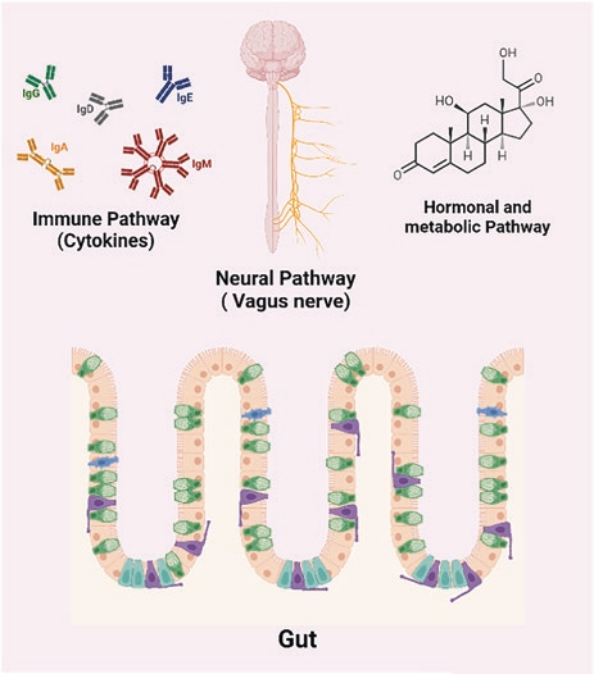

Fig. 7.2 Components of gut-brain access

by manipulating the composition of their gut microbiota (Park and Kim 2021; Bhatia et al. 2023).

7.3 Gut Microbiota in Metabolic Disorders

More than 3 million potentially harmful genes are encoded by up to a thousand bacterial species that live in the human colon. There is a critical function for small molecules generated by gut bacteria. There are substances produced by the microbiota that have been shown to benefit the host. Vitamins, energy sources, compounds with anti-inflammatory, antioxidant, and pain-relieving properties, and molecules that affect the intestinal barrier's function are all examples. However, certain chemicals produced by microbiota may be harmful to the host. These include cytotoxins, genotoxins, and immunotoxins. As a consequence, the gut microbiota is crucial for host physiological function, and dysbiosis of the gut microbiota due to various causes results in profound alterations in host physiology and an elevated risk of metabolic syndrome (MetS) (Fig. 7.1).

7.3.1 Gut Microbiota and Obesity

The expanding medical interest in the diagnosis of MetS is in large part due to the increasing rates of obesity in both Western and non-Western nations. Recent research has demonstrated that there are substantial differences in gut microbiota composition between healthy and obese people, suggesting that gut bacteria may play an important role in obesity (Moran-Ramos et al. 2017).

Obese people with and without type 2 diabetes were studied to learn more about the gut flora in the German population and metabolic disease cohorts. The authors demonstrate a possible link between obesity and changes in the composition, taxonomic dominance, and metabolic functions/outcomes of the microbiome. Serum metabolites associated with gut microbial patterns, including Akkermansia, Fecalibacterium, Oscillibacter, and Alistipes, are significantly altered (Thingholm et al. 2019).

Enterobacter cloacae B29 was isolated from the feces of obese individuals and implanted into germ-free mice by Fei et al. Transplanted mice were obese and insulin-resistant when fed a high-fat diet but not when fed a normal diet. Germ-free mice on a high-fat diet, on the other hand, showed no signs of obesity or insulin resistance. The inflammatory response and blood levels of endotoxin were significantly impacted in fat mice. Obese mice caused by Enterobacter developed a blood endotoxin level and inflammation that proved harmful. These findings point to the gut microbiota as a major environmental factor influencing host fat accumulation and, by extension, the obesity epidemic (Fei and Zhao 2013).

7.3.2 Gut Microbiota and Hyperglycemia

One aspect of MetS is hyperglycemia, which has been linked to gut microbial dysbiosis. The microbiota of four male Zucker diabetic obese rats was recently studied by Zhou et al. Their findings suggest a link between changes in feces microorganisms and the onset of age-related diseases. Between 8- and 15-week-old rats, certain phyla, such as Firmicutes, Bacteroidetes, Actinomicrobiota, and Proteobacteria, made up the bulk of fecal microbes. Among rats aged 8–10 weeks, however, Lactobacillus and Turicibacter were the most common genera. Rats at the 15-week mark had the highest counts of Bifidobacterium, Lactobacillus, Ruminococcus, and Allobaculum. Animals with type 2 diabetes have a slightly altered microbial ecology in their gut microbiome (Zhou et al. 2019). Particularly, in T2DM patients, the prevalence of pathogenic bacteria that are known to cause a variety of different illnesses is elevated, while the prevalence of physiologically beneficial microbiota, such as butyrate-producing bacteria, is decreased (Qin et al. 2012).

7.3.3 Gut Microbiota and Dyslipidemia

Abnormal levels of lipids or lipoproteins in the blood, whether caused by heredity or environmental influences, are known as dyslipidemia. Both in vitro and animal studies suggest that dyslipidemia may lead to dysbiosis of the gut microbiota and that this dysbiosis might exacerbate lipid metabolic diseases. Researchers found that the gut microbiota of C57BL/6 J mice given a high-glucose (HGD) or high-fructose (HFrD) diet was significantly different from that of mice on a normal diet by analyzing 16S rRNA. The results back this up. Both the HGD and HFrD groups were found to have dyslipidemia when no weight change was observed. Mice given HGD or HFrD showed a decreased diversity of gut flora compared to mice on a normal diet. The number of Bacteroidetes was reduced, while the number of Proteobacteria was greatly boosted in the HGD and HFrD groups, respectively. There was also an increase in lipid buildup (Do et al. 2018).

In a comprehensive analysis of 893 people from the Lifelines-DEEP Dutch research cohort, Wang et al. reported on the host genome, gut microbiota (16S rRNA), BMI, and blood lipids. They found that the gut microbiota was responsible for 4.5% of the variation in body mass index, 6.0% of the variation in triglycerides (TGs), and 4% of the variation in high-density lipoprotein (HDL). People with abnormal lipid profiles also have a microbiome in their stomachs that is lacking in microbial diversity. Insight into the connection between blood lipids and gut bacteria is provided by these results (Wang et al. 2016).

7.3.4 Gut Microbiota and Hypertension

The term “dyslipidemia” describes a condition in which there are abnormally high levels of lipids or lipoproteins in the blood. Both in vitro and animal investigations have shown that dysbiosis of the gut microbiota might aggravate lipid metabolic diseases, suggesting a possible link between dyslipidemia and this condition. The gut microbiota of C57BL/6 J mice given a high-glucose (HGD) or high-fructose (HFrD) diet was significantly changed, as revealed by 16S rRNA analysis. The results corroborate this theory. There was no difference in weight between the HGD and HFrD groups, although both had dyslipidemia. Mice given HGD or HFrD showed a less diverse microbiome than those fed a normal mouse diet. Bacteroidetes were in limited supply in the HGD and HFrD groups, but Proteobacteria saw substantial growth. Accumulation of lipids was also seen to be increased (Do et al. 2018).

The host-genome, gut microbiota (16S rRNA), BMI, and blood lipids of 893 people from the Lifelines-DEEP Dutch research cohort were studied in depth by Wang et al. They found that gut microbiota explained 4% of the variation in high-density lipoprotein (HDL), 6% of the variation in triglycerides (TGs), and 5% of the variation in body mass index (BMI). A paucity of microbial diversity was also seen in the gut microbiome of those with abnormal lipid profiles. Therefore, these results

provide insight into the connection between blood lipids and gut bacteria (Wang et al. 2016).

7.3.5 Gut Microbiota and NAFLD

In recent years, NAFLD has surpassed alcoholic liver disease as the most common form of chronic liver disease worldwide. The metabolic syndrome (MetS) is characterized by a cluster of metabolic abnormalities, including abdominal obesity, insulin resistance, type 2 diabetes, and dyslipidemia. NAFLD is a spectrum of liver disorders independently linked with this cluster. The development of NAFLD is heavily influenced by inadequate gut flora.

Yuan et al. found that 35% of Chinese NAFLD patients were associated with high alcohol-producing Klebsiella pneumoniae (HiAlc Kpn). Mice with NAFLD were given HiAlc Kpn isolated in a clinical setting by gavage. Transplanting feces from patients with nonalcoholic steatohepatitis carrying the HiAlc-Kpn strain onto mice resulted in comparable development of NAFLD. The molecular mechanism of NAFLD in mice treated with HiAlc-Kpn may be similar to that of ethanol. Therefore, it is possible that the same chemical pathway as ethanol was responsible for the NAFLD seen in mice administered HiAlc-Kpn. Inflammation and damage to the liver may be caused by bacteria and their metabolites crossing the intestinal barrier and triggering the immune system inappropriately (Yuan et al. 2019). Since the enterohepatic axis links the digestive tract to the liver, it plays an important role in NAFLD's pathogenesis (Zhu et al. 2013).

7.3.6 Gut Microbiota and OSAHS

Unpredictable apneas during sleep and a disturbed sleep cycle define Obstructive Sleep Apnea Hypopnea Syndrome (OSAHS), a sleep condition. OSAHS has been associated with abnormalities in the gut microbiome. Ten mice were exposed to chronic intermittent hypoxia for 6 weeks, and ten mice were given normal oxygen levels; the two groups were compared to one another. In "Quantitative Insights into Microbial Ecology," the authors used 16S rRNA pyrosequencing and bioinformatics to examine the microbiome makeup of mouse feces samples. Mice exposed to intermittent hypoxia had a higher abundance of firmicutes but lower abundances of Bacteroides and proteobacteria compared to controls. Mice exposed to intermittent hypoxia had fecal microbiota composition and diversity changes similar to those seen in patients with OSAHS (Moreno-Indias et al. 2015).

Fecal samples were used by Ko et al. to examine the microbiota makeup of 93 patients with OSAHS and 20 controls. The patient's microbiome has changed, according to functional research, with fewer bacteria generating short-chain fatty acids (SCFAs), more infections, and elevated IL-6 levels. Using a stratified analysis,

they determined that Ruminococcus was the most likely cause of OSAHS. These variations in SCFA concentrations affect the number of pathogens that have a pathophysiological role in OSAHS and associated metabolic comorbidities (Ko et al. 2019).

Human and animal studies have indicated that the processes contributing to MetS symptoms are complex and interconnected. One element in developing MetS is the composition of one's gut microbiome (and its imbalance). Compared to healthy persons, those with MetS have a gut microbiome that is higher in potentially dangerous bacteria and lower in good bacteria. Some bacterial activity, however, may be context-dependent and regulated by host- and microbe-specific factors. According to these characteristics, organisms are classified as either pathogens or symbionts (Zmora et al. 2019).

7.4 Mechanism of Action of the Gut Microbiota with Relation to MetS

7.4.1 Gut Barrier and Inflammation

Numerous investigations have shown that chronic low-grade inflammation characterized by insulin resistance is a fundamental pathophysiological basis of MetS. An imbalance in the gut microbiota and a breakdown of the gut barrier allow bacteria or their components, such as endotoxins, to enter the circulation, where they trigger low-grade inflammation (Hotamisligil 2017).

When the metabolism is functioning normally, gut bacteria regulate intestinal health in a number of ways (e.g., in persons who consume a high-fiber diet). Mucus, antimicrobial peptides, and immunoglobulin A are produced when dendritic cells remove microbial antigens from the intestinal lumen and activate immune cells such as retinoid-related orphan receptor-t dependent T helper 17 and type 3 natural lymphocytes (Natividad et al. 2018).

The intestinal epithelium secretes adenosine monophosphate in response to microbiota metabolites that detect NOD, leucine-rich repeat, and domain-containing protein 3 inflammasomes. The gut microbiota may be detected by its metabolites, which can help maintain the gut barrier (secondary bile acid and aryl hydrocarbon receptor agonist). The intestinal barrier's strength may be affected by both environmental and host-specific factors. Blood insulin levels, which control mucus production through fatty acid synthase, are a part of this (Thaiss et al. 2018).

Environmental and host factors regulate the composition of the microbiota in the digestive tract. Many physiological activities, including the expression of lipopolysaccharide (LPS) and Toll-like receptor signaling, are influenced by the gut microbiota. An imbalance of the gut microbiota may be caused by diet, diarrhea, genetics, and other factors and can lead to metabolic disease (Hoyles et al. 2018).

These changes in the gut cause the translocation of pathogen-associated molecular patterns like LPS and bacterial metabolites like phenylacetic acid, TMA, imidazole propionate, or metabolic disorder mediators, which in turn causes the production of pro-inflammatory cytokines like IL-1 and a state of chronic low-grade inflammation. Host glucose levels trigger barrier breakdown through glucose transporter 2 (Lee et al. 2015).

Further intraluminal causes include the development of exudative diarrhea, which thins mucus and exposes epithelial cells to pathogens, and a rise in bile acid content. Metabolic disease is caused when inefficient metabolism is coupled with inflammation. IL-6 and tumor necrosis factor (TNF) elevations are examples of metabolic inflammation that contribute to the onset of insulin resistance (Natividad et al. 2018).

7.4.2 SCFAs

SCFAs are metabolic byproducts created when bacteria ferment dietary fiber. The liver, fat cells, and intestines all depend on SCFAs to regulate metabolism. SCFAs protect against metabolic illnesses such as obesity, inefficient glucose and lipid metabolism, hypertension, and nonalcoholic fatty liver disease (PYY) by modulating the release of hormones in the intestines (De Vadder et al. 2014).

When there is a positive energy balance (when energy intake exceeds energy expenditure), the buffering capacity of adipose tissue is exceeded, and not all of the excess energy can be stored as TGs. Because of this, blood fat levels rise. Ectopic storage and insulin resistance occur when fat is delivered to non-fat organs such as the liver, skeletal muscle, and pancreas. Short-chain fatty acids (SCFAs) like acetic acid, butyric acid, and propionic acid are produced when the microbes in our gastrointestinal system ferment and break down food but lack the enzymes necessary to complete the hydrolysis (Topping and Clifton 2001).

By modulating the expression of tight junction proteins and mucins, SCFAs may enhance epithelial barrier function and intestinal permeability. If the intestinal barrier is compromised, toxins produced by pathogenic bacteria might make their way into the bloodstream. Audio inflammation, chronic low-grade inflammation and dysfunction, insulin resistance, and weight gain are associated with elevated circulating levels of LPS and other indicators of metabolic endotoxemia (Al-Lahham et al. 2012).

SCFAs may increase insulin sensitivity by enhancing glucose and oxidative metabolism in skeletal muscle. Acetic acid and butyrate promote muscle FA oxidation, perhaps via AMPK activation and PPAR-dependent pathways (Gao et al. 2009).

7.4.3 Bile Acids

Bile acid, an endocrine molecule, controls many metabolic processes. G protein-coupled membrane receptor 5 (GPR5) and farnesol X receptor (FXR) are stimulated by bile acids, which in turn aid in glucose and lipid metabolism (TGR5). Bile acids may also alter the makeup of gut bacteria, as shown by their ability to activate innate immunity genes in the small intestine. This suggests that the microbe's modifications to bile acid may influence host metabolism, which in turn may modify both the makeup of the microbial population and the signals sent by the bile acid receptor (Molinaro et al. 2018).

The production of bile acid is a complex multi-enzyme-regulated process. The production of bile acids occurs in the liver through two distinct mechanisms. At least 75% of all bile acids are produced by cholesterol 7a hydroxylation catalyzed by cholesterol 7-alpha hydroxylase in a healthy organism (CYP7A1). The rate-limiting enzyme CYP7A1 controls bile acid production. Sterol-27-hydroxylase activates a hitherto unexplored metabolic route (CYP27A1). These enzymes' levels of expression are controlled by the gut microbiome (Trabelsi et al. 2015).

Purifying microorganisms stop the small intestine from actively reabsorbing bile acid transporter (ASBT). Bile salt hydrolase (BSH)-active bacteria are responsible for bile acid deconjugation. Metagenomic studies have indicated that BSH is present and functional in all of the major bacterial and archaeal species found in the human gut, including Lactobacilli, Bifidobacteria, Clostridium, and Bacteroides (Jones et al. 2008).

Incorporating natural bile acids as FXR activators may lead to the production of TGR5 ligands by gut bacteria, highlighting the need to investigate the microbiota of the digestive tract. Inflammation in adipose tissue is induced by the gut microbiota through an FXR-dependent pathway as a result of increased expression of genes involved in fat absorption in the liver. The relationship between bile acids and bacteria is dynamic. This correlation may have beneficial or negative consequences on the host's metabolism, depending on dietary changes. Metabolic illness may result from crosstalk between the microbiome and the host's metabolism through bile acids, FXRs, TGR5, and other microbially derived compounds (Wang et al. 2020).

7.5 Gut Microbiota-Targeted Therapies in MetS

7.5.1 Probiotics and Prebiotics

As a kind of microbiota management treatment, probiotics and prebiotics are used to boost host health. Probiotics are bacteria that provide a health benefit to the host when supplied in enough proportions. Probiotics improve the host through interacting with the host and its microbiota, increasing the diversity of gut bacteria and stimulating the host's immune system (Tenorio-Jiménez et al. 2019).

Tenorio-Jimenez et al. reported on probiotics and MetS research, including 53 adults with a recent MetS diagnosis. Patients were split into two groups based on their body mass index and gender. For 12 weeks, those in the study's experimental group received a pill containing Lactobacillus reuteri V3401, whereas those in the placebo group did nothing. In this study, researchers looked at a variety of factors, including body composition, biochemical and inflammatory markers, and the composition of the gut flora. Both groups had the same MetS clinical symptoms. The levels of IL-6 and soluble vascular cell adhesion molecule-1 were significantly lower in the experimental group compared to the control group (Tenorio-Jiménez et al. 2019).

Unfortunately, prebiotics are not tolerated or absorbed by the host. By influencing digestion favorably, they are effective. It has been shown that prebiotics like glucans and fructose are helpful to the host because they stimulate the development of helpful bacteria while suppressing the formation of dangerous germs (Tenorio-Jiménez et al. 2019).

Patients with type 2 diabetes were split into two groups, according to Zhao et al. The control group received the usual medical attention, whereas the experimental group was given a high-fiber diet with Chinese herbs, whole grains, and prebiotics. Acarbose was given as a regular medication to both groups. Significant and time-dependent reductions in glycated hemoglobin (HbA1c) levels were seen in both groups by day 28; however, the experimental group had a quicker reduction in HbA1c levels. The rate of blood glucose control (HbA1c 7 percent) at the end of the study for the experimental group was similar to that of the control group. More weight was lost, and improved blood lipid levels were seen in the experimental group compared to the control group. Before and after intervention, the same people's gut microbiota was collected for transplantation into germ-free C57BL/6 J mice. Prior to the intervention, both groups' metabolic health markers were better than mice's. Increased levels of SCFA-producing bacteria are directly related to better control of blood glucose levels, as shown by the overexpression of GLP-1. While it's true that some research has demonstrated that probiotics and prebiotics may have positive effects on the host, this evidence is mixed; the outcomes of the experiments have been challenged, and there is no definitive recommended benefit. Thus, further clinical trials are needed to fully understand the potential of probiotics and prebiotics in the treatment of MetS (Zhao et al. 2018).

7.5.2 FMT

FMT stands for "gut microecological transplantation," and it's used to treat GI and parenteral diseases by re-establishing a healthy microbiota in a patient's digestive tract through their feces. Recently, fecal microbiota transplantation (FMT) has been the topic of much discussion after the publication of a few particularly prominent publications in the scientific literature. Studies have demonstrated that FMT is effective against recurrent Clostridium difficile infection (Levy et al. 2015).

These results suggest that FMT therapy may be useful for metabolic syndrome and type 2 diabetes. Recent studies have revealed that FMT through gastroduodenal tube from lean donors to obese persons with metabolic syndrome significantly improves the recipients' insulin sensitivity (Henao-Mejia et al. 2012).

After 6 weeks of therapy, fecal SCFA levels decreased while microbial diversity rose, and the fraction of butyrate-producing Roseburia intestinalis increased by 2.5-fold. Despite this first clue that such an approach might be positive, larger, better-designed trials are required to examine if such medicines are typically effective for those with metabolic syndrome or T2DM.

7.5.3 Metabolic Surgery

Obesity's systemic signs, such as high blood pressure, high cholesterol, and high glucose, are all treatable with medication. In metabolic surgery, the gastrointestinal system is rearranged in ways that alter nutrient absorption, gastric emptying, gastric acid production, gut flora, and cholic acid composition (Anhê et al. 2017).

Bile acid shunting, stomach reduction, intestine rerouting, vagus nerve modulation, and gastrointestinal hormone management are all common procedures in metabolic surgery. After metabolic surgery, the population of bacteria that produce butyric acid may decrease while the population of Proteobacteria grows. Thus, after metabolic surgery, there may be changes in the composition of gut microbiota and the production of functional products (such as endotoxins, bile acids, and branched-chain amino acids) (Debédat et al. 2019; Seganfredo et al. 2017).

De Jonge et al. discovered that a non-surgical duodenojejunostomy bypass was effective in treating type 2 diabetes in 17 morbidly obese patients. Weight and glycosylated hemoglobin levels improved after 6 months of therapy in this study. Changes occurred in the regularity with which tiny intestinal bacteria were excreted in the stool. There were more Proteobacteria, Veillonella, and Lactobacillus species than normal in the waste. However, several reports suggest that bacteria eventually return to their pre-intervention levels after some time has passed. Some processes that may lead to weight loss after metabolic surgery include a smaller stomach size and a change in the concentration of gut peptides. Some patients report weight loss following metabolic surgery due to a return to normal levels of gut flora. Studies with large samples are needed to prove that gut microorganisms have a role in recovery after metabolic surgery (De Jonge et al. 2019).

7.6 Bidirectional Communication Pathways

7.6.1 Neural Pathway (Vagus Nerve)

The vagus nerve, the longest of the cranial nerves, links the brainstem to the digestive system, creating a neurological relationship known as the gut-brain axis. The vagus nerve connects the gut to the brain and functions as a two-way information highway. This improves coordination and communication between the two bodies (Fülling et al. 2019).

The gut-brain axis neural network is a complex and dynamic system that has far-reaching effects on health and well-being. Symptoms such as digestive distress, metabolic disorders, and mental health issues have all been linked to disruptions in the vagus nerve and the neurological pathway of the gut-brain axis (Browning et al. 2017).

As a result, the vagus nerve and the neurological route of the gut-brain axis have been the focus of increased investigation and development in recent years. Vagus nerve stimulation, nutritional treatments, probiotics, and other microbiome-based therapies may be utilized in combination with behavioral therapy targeted at reducing stress and improving relaxation (Breit et al. 2018).

A major component of the parasympathetic nervous system, the vagus nerve is a part of the gut-brain axis. The parasympathetic nervous system is one of the two branches of the autonomic nervous system, which regulates processes like heart rate, breathing, and digestion without conscious involvement (Forsythe et al. 2014; Longo et al. 2023).

Information about the state of the digestive system and the presence of food and potentially hazardous or useful chemicals is sent to the brain through the vagus nerve (Cork 2018).

The vagus nerve relays information from the intestines to the brain, including the presence of food, the strain on the intestinal wall, and the presence of potentially hazardous or useful compounds (Fornai et al. 2018; Xj et al. 2020).

For instance, vagus nerve stimulation has been shown to be effective in the treatment of depression, anxiety, and other mental health concerns by modulating the function of brain areas responsible for emotion control and stress response (Longo et al. 2023).

7.6.2 Hormonal Pathway (HPA Axis)

Communication between the digestive system and the brain occurs through a hormonal pathway known as the gut-brain axis, which is essential to good health (Appleton 2018). Because it allows for information to be sent between the digestive system and the brain, the hormonal pathway of the gut-brain axis is essential to good health. Since dysregulation of this system has been linked to a variety of health

issues, there is a rising interest in creating novel treatments that target the HPA axis to improve health and well-being (Kumsta et al. 2017). The HPA axis is a hormonal and neural pathway that regulates the body's reaction to stress (Rusch et al. 2023).

The body's stress response is regulated by the hypothalamic-pituitary-adrenal (HPA) axis. When the brain releases CRH under stressful situations, the pituitary gland responds by releasing adrenocorticotropic hormone (ACTH) (ACTH). The adrenal glands release the stress-reducing hormone cortisol when ACTH is present (Sudo 2014).

The hormonal route of the gut-brain axis produces a variety of signaling molecules that may influence both gut and brain function. These molecules include hormones, cytokines, antidepressants, glucocorticoid receptor antagonists, and neurotransmitters (Mittal et al. 2017).

The stress hormone cortisol is just one of the hormones involved in the gut-brain axis; the sympathetic nervous system also contributes adrenaline and noradrenaline. Changes in intestinal motility and vascularity maybe two ways in which these hormones affect gastrointestinal function (Cussotto et al. 2018).

The neurotransmitters serotonin, dopamine, and gamma-aminobutyric acid are all part of the hormonal route along the gut-brain axis (GABA). The effects of neurotransmitters, chemicals produced by the brain and the digestive tract, may be felt all throughout the body. Serotonin, for instance, regulates not just hunger but also digestion and secretion, as well as mood and behavior (Mittal et al. 2017).

The HPA axis regulates several bodily functions, including metabolism, immune system response, and stress response. Several signaling molecules, including cortisol, cytokines, and neurotransmitters, are produced by the HPA axis and may affect the gut function and the microbiota (Appleton 2018).

Understanding the hormonal route of the gut-brain axis is crucial if we want to boost the health and happiness of the population as a whole. Stress management treatments like cognitive behavioral therapy and mindfulness meditation may be used in tandem with anti-HPA axis medications to get optimal results (Breit et al. 2018; Dong and Gupta 2019).

7.6.3 Immune Pathway (Cytokines)

Cytokines, a type of signaling proteins involved in the gut-brain axis' immunological pathway, are produced by immune cells in response to infection or inflammation. Modulating the HPA axis and neurotransmitter systems, these cytokines may also influence cognitive and behavioral functions (Petra et al. 2015). Lymphocytes such as T cells, B cells, and natural killer (NK) cells, in addition to macrophages and dendritic cells, may play a role (Powell et al. 2017).

Cytokines are important signaling molecules in the gut-brain axis of the immune system. In response to an infection or inflammation, immune cells release cytokines that have the potential to alter immune system and nervous system activity,

therefore impacting gastrointestinal and central nervous system processes (Sherman et al. 2015).

Cytokines are a family of molecules that play a significant role in the gut-brain axis of the immune system. The immune system produces cytokines in response to infection or inflammation; these cytokines may affect the gut and the brain by altering the functioning of the immune and nervous systems (Rutsch et al. 2020; Rieder et al. 2017).

The gut microbiota has a role in the immune system that is comparable to that of the gut-brain axis. Immune system function may be altered by the gut microbiota due to the production of metabolites and signaling molecules that may interact with immune cells (Generoso et al. 2020).

Disruptions in the immunological system between the gut and the brain have been linked to a variety of illnesses, including inflammatory bowel disease, autoimmune disorders, anxiety, and depression (Martin-Subero et al. 2016). Dysregulation of the immune system may originate from changes in gut function and the makeup of the microbiota, which has been related to chronic inflammation in the gut. Anxiety and sadness, as well as inflammatory bowel disease (IBD) and other gastrointestinal illnesses, may develop as a consequence (Abautret-Daly et al. 2018).

7.6.4 Metabolic Pathway (Short-Chain Fatty Acids)

Bacterial metabolites have strong effects on the humoral system (particularly short-chain fatty acids [SCFAs], produced by bacterial fermentation of dietary carbohydrates). These chemicals modulate the immune system, connect with nerve cells through the sympathetic branch of the autonomic nervous system, and modify enterocyte feeding (Appleton 2018).

SCFAs created from the microbiota have been found to pass the blood-brain barrier, and microglia homeostasis is crucial for proper brain development, brain tissue homeostasis, and behavioral regulation. Disruptions in SCFA metabolism are significant because they have been linked to the development of autism through interfering with microglial communication and function (Rogers et al. 2016; Parker et al. 2020).

Studies have demonstrated that SCFAs impact the hormonal communication between the gut and the brain by influencing the production of gut-derived serotonin by enterochromaffin cells and the release of gut-derived peptides by enteroendocrine cells (Mirzaei et al. 2021). About 95% of serotonin is found in plasma, with the remaining 5% being made in the intestines. The effects of serotonin on afferent nerve terminals involved in digestion and peripheral metabolism are distinct from its effects on the central nervous system (Martin et al. 2017).

Many doctors are unaware that autistic children have higher plasma serotonin levels despite the fact that they understand the mechanism by which fluoxetine blocks the absorption of serotonin in the intestines. In young boys with ASD,

elevated plasma serotonin levels are counterbalanced by reduced serotonergic neurotransmission (Appleton 2018).

Lipopolysaccharide, an important bacterial molecule, is mostly produced by Gram-negative enterobacteria and is found in their cell walls (LPS). Leaky gut syndrome is caused by defects in the tight junctions between intestinal epithelial cells, which allows LPS to enter the bloodstream. Anti-LPS antibodies are naturally produced by the body; nevertheless, they are more common in people with serious depression than in controls (Appleton 2018).

7.7 Gut Microbiota Composition and Diversity

7.7.1 Factors Affecting Gut Microbiota

7.7.1.1 Genetics

The diverse colony of bacteria that calls your digestive tract home (the gut microbiota) is crucial to your health. In addition to environmental influences, including nutrition, medicine, and stress, genetics may also influence the makeup and function of the gut microbiota (Cong et al. 2016). Evidence suggests that the gut microbiota may be influenced by a complex set of genetic factors. The genetic makeup of the host is an important factor. Some genetic polymorphisms have been related in research to differences in the composition of the gut microbiota. Genetic variations in immune system genes and bile acid metabolism genes, among others, have been linked to the gut microbiota (Hall et al. 2017).

By inhibiting the growth of potentially harmful microorganisms and encouraging the growth of good ones, the immune system plays a crucial role in regulating the gut microbiota. Immune-related gene variations have been linked to dysbiosis because they disrupt this equilibrium (Rieder et al. 2017).

In addition to host genetics, epigenetic alterations may affect the gut flora. Changes in gene expression may be made epigenetically rather than by altering the DNA sequence. Changes in DNA methylation and chromatin state have been linked to alterations in the gut microbiota. Changes in the FUT2 gene's DNA methylation status have been linked to variations in the gut microbiota. Mucin, a key component of the intestinal barrier, is produced by this gene (Kurilshikov et al. 2017).

There is not just one way in which genetics and gut bacteria interact. However, genetics may have direct effects on the gut microbiota via modifications to the host's immune function and bile acid metabolism. There may be more ways in which the gut bacteria influences host gene expression (Zheng et al. 2020).

Understanding the role of genetics in creating gut microbiota is necessary for the development of innovative therapies that target the microbiota to promote health and prevent illness. In addition to dietary modifications, probiotics, and other treatments based on the microbiome, stress reduction and healthy lifestyle promotion behavioral methods may be helpful. Understanding the genetic basis of various

diseases linked to dysbiosis and altered gut microbiota has the potential to lead to the creation of personalized therapies that target certain genetic variations (Hooks et al. 2019).

Diet

A person's food has a major impact on the microorganisms in their gut. What and how much is eaten may influence the make-up and function of the gut microbiota. The quantity of good bacteria in the gut, such as Bifidobacterium and Lactobacillus, rises when the diet is rich in fiber and plant-based foods, whereas the number of Firmicutes and Enterobacteriaceae decreases (Cresci and Bawden 2015).

These probiotic microorganisms aid in the formation of short-chain fatty acids (SCFAs), which are essential for digestive and immune system function. A dysbiosis, or imbalance in the gut microbiota, where dangerous bacteria overgrow, may result from a diet high in processed foods, sugar, and fat (Albenberg and Wu 2014).

Dysbiosis has been related to inflammatory bowel disease, obesity, and even neurological disorders. Changing one's diet has been shown to have a rapid and reproducible effect on the gut microbiota's makeup and function (Flint et al. 2015).

Medications

The medicine may alter the bacteria in the gut significantly. Antibiotics are only one kind of medication that has the potential to wipe off beneficial microorganisms, leaving the body wide open to potentially devastating opportunistic illnesses. Other drugs than antibiotics and antidepressants have been demonstrated to change the makeup of gut flora as well, such as proton pump inhibitors and NSAIDs (Weersma et al. 2020).

There may be substantial alterations to the gut microbiota as a result of medication treatment. Medicines like antibiotics, for example, may wipe off beneficial bacteria and leave the body open to potentially devastating opportunistic infections. Other pharmaceuticals that have been proven to change the makeup of gut flora include proton pump inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs), and antidepressants. Antibiotics are only one kind of medication that might alter the microbiome of the digestive tract. Antibiotics may treat bacterial illnesses, but they have the potential to wipe off the good bacteria already present in your digestive system. Possible side effects include diarrhea, yeast infections, and antibiotic resistance due to disruption of the microbiota's delicate balance (Yang et al. 2021a).

Acid reflux disease (GERD) and other disorders caused by excess stomach acid are often treated with proton pump inhibitors (PPIs). Altering stomach acid production with proton pump inhibitors (PPIs) changes the gut microbiota (Imhann et al. 2017). Evidence suggests that proton pump inhibitors (PPIs) may alter the gut microbiota by decreasing the population of beneficial bacteria (Macke et al. 2020).

Nonsteroidal anti-inflammatory medications (NSAIDs) like aspirin and ibuprofen are often used to relieve pain and inflammation. However, it's possible that these drugs might alter the microbiota in the digestive tract (Zádori et al. 2022). Evidence suggests that nonsteroidal anti-inflammatory drugs (NSAIDs) may alter the microbiota of the stomach, altering the balance between helpful and harmful microorganisms (Bindu et al. 2020; Maseda and Ricciotti 2020).

Antidepressants may also have an effect on the microbiota of the digestive tract. Some studies have shown that antidepressants, potentially influencing the central nervous system and the immune system, may modify the gut flora (Lukić et al. 2019).

7.8 Intestinal Microbial Community Discord (Dysbiosis)

The global frequency of several immune-mediated, metabolic, neurodegenerative, and mental disorders is rising. The higher the morbidity rate of a population, the more vulnerable it is to external stresses like the spread of infectious diseases. Alterations to the microbiome of the gut have been linked to many of these diseases in recent years (Saklayen 2018).

Many of these diseases have been related to dysbiosis or abnormalities in the gut microbiota's composition and function. Dysbiosis manifests itself via changes to the microbiome, such as fewer species of bacteria, fewer helpful bacteria, or an increase in dangerous microbiota. The digestive system is home to a wide variety of microorganisms, including bacteria, fungi, protists, archaea, and viruses (Fan and Pedersen 2021).

Researchers looked at everything that may have an effect on gut microbiota and how to fix dysbiosis. Hope for the future development of microbiota-based therapies (Hrncir et al. 2019) like FMT or probiotics rests on the fact that a healthy gut microbiome can be restored. There are many potential causes of dysbiosis, but lifestyle and cleanliness are two of the most important ones to investigate (Afridi et al. 2021).

Changes in macronutrients may rapidly and significantly alter the composition of the stomach's resident bacteria and fungi. The intestinal barrier is compromised, intestinal inflammation is triggered, and the host's metabolism is slowed by high-simple-carbohydrate diets (Hrncir et al. 2021). It is the interactions between food and bacteria that are mostly responsible for the unfavorable impacts, such as the inability to manifest in a germ-free state without the gut microbiota and the transfer of the disease phenotype upon gut microbiota transplantation (Hrncirova et al. 2019).

Recent studies have shown that popular food preservatives may cause an overgrowth of proteobacteria and that some human gut microbiotas are more susceptible to these chemicals; our results are in line with those of other groups working in this field (Vrieze et al. 2012).

In SAMP1/YitFc (SAMP) mice, artificial sweeteners like Splenda exacerbate ileitis by promoting proteobacterial dysbiosis (Chassaing et al. 2017). Artificial sweeteners like Splenda, which promote proteobacterial dysbiosis, exacerbate ileitis in SAMP1/YitFc (SAMP) mice (Rodriguez-Palacios et al. 2018).

However, studies have revealed that non-caloric sweeteners actually promote dysbiosis and glucose intolerance in a microbiota-dependent manner despite being designed to avoid metabolic syndrome (Suez et al. 2014).

Gut microbiota load and composition may be influenced by host-derived factors such as antimicrobial compounds produced by path cells, including defensins, lysozymes, and antibacterial lectins (Reg3), or SIgA produced by plasma cells (Catanzaro et al. 2019).

Alterations to the gut and disruptions to the intestinal barrier and the host's immune and metabolic systems are only two examples of the many consequences of microbial ecology. Acetaldehyde generation from exogenous or endogenous ethanol, direct mucolytic activity, and other activities may all contribute to the microbiota's ability to impair the intestinal wall's integrity. There is evidence that inflammasome signals from Toll-like receptors (TLRs) and NOD-like receptors (NLRs) are used by the microbiota to control the host immune system (Lee et al. 2020).

Another tactic is to alter the balance of regulatory to proinflammatory immune cells. Choline to trimethylamine (TMA) generation, changes in bile acid composition, and SCFA formation from dietary fiber all affect human metabolism, especially glucose and lipid metabolism (TMA) (Karlsson et al. 2013).

Studies of the gut microbiota, its metabolites, and the hosts they interact with may lead to the development of novel diagnostic and therapeutic approaches. Tissue biopsies and other invasive diagnostic procedures are often used for purposes such as diagnosis, subtype identification, monitoring the course of illness, and evaluating the efficacy of treatment. The importance of reliable, non-invasive indicators is highlighted. Some metabolites and gut microbes have been shown in recent research to offer potential as diagnostic and prognostic indications (Aron-Wisnewsky et al. 2019).

Several bacterial metabolites have diagnostic potential. The metabolites succinate, phenylacetic acid, and 3-(4-hydroxyphenyl)-lactate are all useful in the diagnosis of liver problems. NAFLD patients' fecal, serum, and liver samples showed a rise in the prevalence of NAFLD-associated bacteria such as Bacteroidaceae and Prevotella, and blood phenylacetic acid levels correlated with hepatic steatosis severity (Chu et al. 2019).

The gut microbiota may be used in a variety of medicinal contexts. For instance, transplanting fecal microbiota might aid in re-establishing the balance of the microbiome as a whole (FMT). Restoring lost functions may be accomplished by reinstating beneficial strains or communities of strains (probiotics) to the gut microbiota while eliminating toxic or undesirable strains (with antibiotics, antifungals, or bacteriophages). Finally, by inhibiting or activating certain metabolic pathways, detrimental microbial metabolites may be reduced while beneficial ones are enhanced (Caussy et al. 2018).

Therapeutic strategies that modify the microbiome to increase the synthesis of protective metabolites or decrease the creation of harmful metabolites hold great potential. The structural counterpart of choline, 3,3-dimethyl-1-butanol, is used to stop bacteria from turning choline in the diet into TMA. When TMA is oxidized, a

compound called trimethylamine N-oxide (TMAO) is produced. TMAO has been related to atherosclerosis and other potentially fatal cardiovascular diseases (Hvas et al. 2020).

Recurrent Clostridioides difficile infection (CDI) can be cured with FMT 90% of the time, making it a potentially lifesaving therapy. FMT is the first line of treatment for CDI since most patients show improvement after only one session (Brandt et al. 2011). Pharmaceutical companies, however, are actively lobbying to get FMT categorized as a drug so that they may corner the market. Ulcerative colitis, constipation, irritable bowel syndrome, liver disorders including cirrhosis with encephalopathy and alcoholic hepatitis, and neurological ailments like multiple sclerosis and Parkinson's disease have all been treated with FMT in experimental settings (Xue et al. 2020).

Intestinal microbiota and host health may be altered with the use of probiotics. The many beneficial effects of probiotic bacteria probably have some common pathways. Important mechanisms include control of the immune system and resistance to intestinal colonization (neurochemicals, hormones), as well as the production of metabolites with local (antimicrobials, enzymes, organic acids) and systemic (antibodies, hormones) effects (Sanders et al. 2019).

Mounting evidence suggests that the gut microbiota is involved in a wide range of immune-mediated, metabolic, and neurological illnesses. The gut microbiome may be severely altered by factors such as diet (particularly if it's unhealthy) and medication. Given how persistent these disorders are, it's likely that heredity plays little influence in their development. The intestinal barrier may be compromised by a microbiota in dysbiosis, resulting in an excess of food and microbial compounds that may have deleterious effects on the host's immune system and metabolic processes. The development of efficient microbiota-based treatments will also benefit from a comprehensive understanding of microbiota-host interactions. These procedures may include the transplanting of the fecal microbiota or the introduction of new, beneficial strains to the microbiome. Altering the pace at which microbes produce their own metabolites is yet another option.

7.9 Microbiota in the Gut and Mental Illness

7.9.1 Depression

7.9.1.1 Preclinical

Preclinical studies have linked alterations in gut microbiota and microbial metabolites to the etiology of depression at the cognitive level—the connection between the stomach and the microbes that live there (Mitrea et al. 2022). Gut bacteria may create neurotransmitters like serotonin, which aid in mood control (Skowronska et al. 2023). Dysbiosis of the gut microbiome has been linked to mental health issues in animal models (Skowronska et al. 2023; Guo et al. 2019).

One preclinical study using Bifidobacterium teenagers found that the bacteria helped relieve anxiety and depression by decreasing inflammatory cytokines and resetting the gut microbiota (Guo et al. 2019). Butyrate and other SCFAs have been shown to be well-established inhibitors of histone deacetylase in various studies. By inhibiting histone deacetylases, SCFAs may boost the expression of synaptic plasticity- and neuroprotection-related genes, which may lead to an improvement in mood (Skowronska et al. 2023; Guo et al. 2019).

7.9.1.2 Clinical

The benefits of probiotics on mood disorders have been studied in clinical trials. Patients with major depressive disorder who were not receiving any treatment saw improvements in their affective clinical symptoms and subjective sleep quality after taking a probiotic supplement containing the bacteria Lactobacillus helveticus R0052 and Bifidobacterium longum R0175, according to the results of an open-label pilot study (Wallace and Milev 2021). Histone deacetylase is an enzyme that has been shown to be inhibited by SCFAs and butyrate, according to the previous study. By inhibiting histone deacetylases, SCFAs may boost the expression of synaptic plasticity- and neuroprotection-related genes, which may lead to an improvement in mood (Rahimlou et al. 2022).

Clinical studies have shown that the gut microbiota affects the brain predominantly via the vagus nerve and humoral transmission (Chang et al. 2022). Schiopu et al. suggest that the gut microbiota may influence CNS function through metabolic and neuroendocrine pathways (Schiopu et al. 2022). Multiple studies have shown an association between dysbiosis in the microbiome and epigenetics and the onset of depression (Schiopu et al. 2022).

7.9.1.3 Potential Mechanisms

Several pathways between the gut microbiota and depression exist.

- Gut bacteria may produce chemicals like serotonin, which regulate mood, by acting as a factor (Yoo et al. 2022; Alli et al. 2022).
- Inflammation: Abnormalities in the microbiota-gut-brain axis are emerging as a potential contributor to the pathophysiology of depression. Inflammatory substances generated by the gut microbiota and subsequently transferred to the brain may have a role in the development of depression (Caspani et al. 2019; Eltokhi and Sommer 2022).
- Oxidative stress: Increased oxidative stress has been linked to cognitive decline in depressed people (Dobielska et al. 2022).
- Depression is associated with hypothalamic-pituitary-adrenal axis abnormalities, which have been linked to cognitive decline and worse social functioning. Depressed people are more likely to have declines in cognitive ability, although

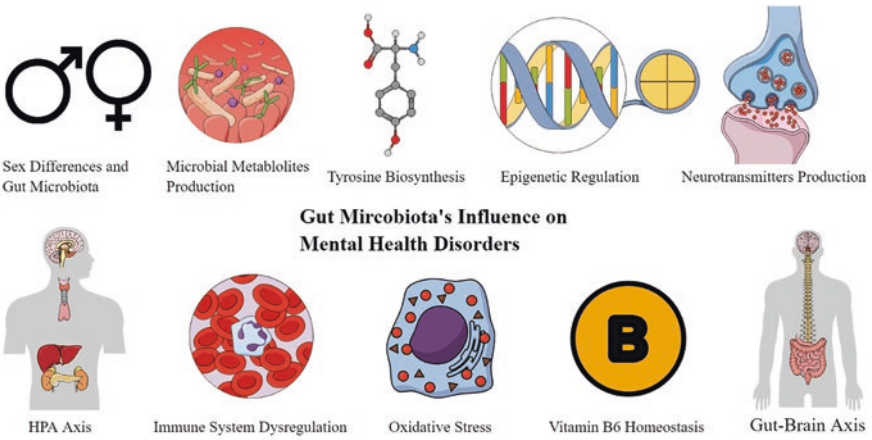

Fig. 7.3 Gut microbiota's influence on mental health disorders

these problems are generally ignored by psychiatrists. Therefore, this problem necessitates a more biomolecular and systemic approach, as well as the creation of superior therapeutic methods (Dobielska et al. 2022).

- Epigenetic regulation: Disruptions in the hypothalamic-pituitary-adrenal axis have been linked to depression, which may lead to a reduction in cognitive ability and subsequent effects on social functioning. Mental health professionals frequently ignore the fact that depressed patients are more prone to have declines in cognitive function. This calls for a rethinking of both biomolecular and systemic approaches to therapy (Caspani et al. 2019).

The gut microbiota may have a role in depression via epigenetic regulation, inflammation, oxidative stress, alteration of the hypothalamic-pituitary-adrenal axis, and the production of neurotransmitters. More research is needed to better understand the links between the gut microbiota and the central nervous system and to develop innovative therapeutic approaches to depression (Fig. 7.3).

7.9.2 Anxiety

7.9.2.1 Preclinical

Changes in gut flora have been related to anxiety-like behavior in animals, according to a preclinical study. Dysbiosis, or an imbalance in the gut microbiota, has been related to anxious behavior in rats (Clapp et al. 2017; Simpson et al. 2021). Researchers have shown that anxiety-like behavior is reduced in germ-free (GF) mice compared to conventionally raised mice (Clapp et al. 2017; Huang and Wu 2021). In addition, various probiotics have been proven to reduce nervous behavior

in experimental animals (Bibbò et al. 2022). These findings from nonhuman primates suggest that gut microbiota may affect nervous behavior in humans.

7.9.2.2 Clinical

Clinical studies have examined the connection between anxiety and the microbiota in the digestive tract. Recent studies have linked changes in gut microbiota caused by indoxyl sulfate to the emergence of psychological symptoms (namely, anxiety) in humans. Thus, changes in the gut microbiota may lead to the development of neuropsychiatric disorders, necessitating a range of therapeutic and treatment strategies (Brydges et al. 2021). Anxiety and sadness, among other mental health issues, were linked to changes in the gut flora, according to another research (Huang and Wu 2021). Recent studies have shown that social anxiety disorder is associated with alterations in the gut flora (Butler et al. 2023). This study's findings provide support to the idea that bacteria in the digestive tract may have a role in human anxiety.

7.9.2.3 Potential Mechanisms

Not all the mechanisms through which the gut microbiota affects anxiety have been identified. However, other processes have been proposed. One such hypothesized mechanism is the gut-brain axis, the two-way channel of communication between the digestive system and the brain (Clapp et al. 2017; Foster et al. 2017). Potential effects of microbes on the human brain and behavior (Clapp et al. 2017; Foster et al. 2017). Stomach bacteria produce neurotransmitters and other signaling substances that may have an effect on the brain and behavior (Huang and Wu 2021). Alterations in immune function and inflammation are also linked to anxiety, and the microbiota in your gut may have a hand in that (Clapp et al. 2017). Chemicals produced by the gut microbiota may also affect mental and behavioral functions (Ferrarelli 2022). Anxiety has been related to the hypothalamic-pituitary-adrenal (HPA) axis, which is implicated in the stress response (Clapp et al. 2017). More research is needed to fully understand the mechanisms through which gut bacteria may affect anxiety (Fig. 7.3).

7.9.3 Autism Spectrum Disorder

7.9.3.1 Preclinical

Preclinical studies have shown that gut microbiota may influence brain development and behavior through the neuroendocrine, neuroimmune, and autonomic nervous systems (Li et al. 2017). Changes in the composition of the gut microbiota and the production of bacterial metabolites have been linked to autism spectrum

disorder (ASD) (Roussin et al. 2020). Evidence of dysbiosis and bacterial metabolite changes in ASD has been discovered in both clinical and preclinical studies (Roussin et al. 2020). In animal models of autism, microbial probiotics have shown some promise in correcting ASD behavior and altering the integrity of the gastrointestinal epithelial barrier (Wong et al. 2021).

7.9.3.2 Clinical

Clinical studies have shown that persons on the autism spectrum are more likely to have digestive problems than the general population (Roussin et al. 2020). Those on the autistic spectrum may be more likely to have gastrointestinal problems due to a disruption in the normal composition of their gut bacteria (Wong et al. 2021). Clinical studies show that individuals on the autism spectrum are more prone to have digestive problems than the general population (Wong et al. 2021).

7.9.3.3 Potential Mechanisms

Several ways exist through which the gut microbiome may impact autism spectrum disorder:

- Immune system dysregulation: Changes in gut microbiome composition have been connected to the pathophysiology of gastrointestinal symptoms in individuals with autism spectrum disorder in a number of studies, both in people and animals (Liu et al. 2022). The development of autism spectrum disorder (ASD) has been related to immune system modulation by gut bacteria (Garcia-Gutierrez et al. 2020).
- Metabolite production: Gut microbiota-derived metabolites have the potential to influence immunological function and the brain's circuitry (CNS) (Garcia-Gutierrez et al. 2020). Clinical and experimental studies have shown that people with ASD have different compositions of gut microbiota and the metabolites they produce (Roussin et al. 2020).
- Neurotransmitter production: The development and behavior of the brain are influenced by neurotransmitters secreted by gut bacteria (Li et al. 2017). ASD has been associated with altered bacterial metabolite production and alterations in the composition of the gut microbiota (ASD) (Roussin et al. 2020).
- Vitamin B6 homeostasis: In EphB6-deficient mice, the gut microbiota mediates vitamin B6 homeostasis, allowing for the control of autistic-like behavior (Li et al. 2020).
- Gender bias: The gut microbiota may have a role in sex differences in ASD through metabolites, immunology, and genetics (Hao et al. 2020).

In conclusion, the gut microbiota has been linked to ASD development via many potential mechanisms, including immune system dysregulation, metabolite synthesis, neurotransmitter production, vitamin B6 homeostasis, and gender bias. More

research is needed to fully understand the complex relationship between gut microbes and ASD (Fig. 7.3).

7.9.4 Schizophrenia

7.9.4.1 Preclinical

The gut microbiota may have a role in the pathogenesis of schizophrenia (SZ) through the gut-brain axis (Yuan et al. 2021). The gut-brain axis has been known for a long time to be a communication link between the microbes in the intestines and the brain (Munawar et al. 2021). Schizophrenia risk factors have been proposed to include changes in the gut microbiota's makeup and activity (Kelly et al. 2021a). Brain function and behavior may be influenced by bacteria in the gut (Zheng et al. 2019). Schizophrenia patients' gut flora influences the glutamate-glutamine-GABA cycle (Zheng et al. 2019).

7.9.4.2 Clinical

The importance of the gut microbiota to the etiopathogenesis of mental diseases has been shown in several research (Tsamakis et al. 2022). A link between gut microbiome formation and schizophrenia risk has been shown in several studies (Nuncio-Mora et al. 2023). Individuals with schizophrenia have been shown to have a significantly different gut microbiota makeup compared to those without the disorder (Nuncio-Mora et al. 2023). In schizophrenia, the gut microbiota is linked to cognitive performance (Li et al. 2021a). Intriguingly, recent research indicates a similar pathophysiology between schizophrenia and obesity and an imbalance in the gut microbiota as the root cause (Khaity et al. 2023; Wu et al. 2023).

7.9.4.3 Potential Mechanisms

Potential implications for schizophrenia arise from the two-way communication between the gut bacteria and the brain (Thirion et al. 2023) and (Munawar et al. 2021). There may be a link between changes in the gut flora and symptoms of schizophrenia (Singh et al. 2022) (Fig. 7.3).

7.9.5 Other Mental Health Disorders (E.g., Bipolar Disorder, ADHD)

Recent studies have shown a link between abnormalities in the gut microbiota and the gut-brain axis and attention deficit hyperactivity disorder (ADHD) (Dam et al. 2019; Sukmajaya et al. 2021; Schleupner and Carmichael 2022). Mood fluctuations in people with bipolar disorder (BD) may be moderated by metabolites produced by their gut microbes (Zhang et al. 2022; Gondalia et al. 2019; Ortega et al. 2023; Lucidi et al. 2021). However, there has been less research on the roles of gut bacteria in mental disorders, including bipolar disorder and attention deficit hyperactivity disorder. FMT, or fecal microbiota transplantation, has recently demonstrated promising benefits for individuals with treatment-resistant bipolar disorder (Parker et al. 2022). In addition, research has connected a healthy, diverse gut microbiota to fewer health problems, including a reduced chance of developing ADHD (ADHD) (Cassidy-Bushrow et al. 2023).

7.10 Definition of Probiotics and Prebiotics

Some types of living microorganisms, called probiotics, are helpful to the health of the host organism when administered in sufficient numbers. Although fermented foods are a good source of these bacteria, you can also add them to other foods or purchase them as dietary supplements. The effects of probiotics have rapidly spread from the digestive system to other organs and systems, including the neurological system (CNS) (Snigdha et al. 2022). Neurological illnesses, such as Alzheimer's disease (AD), autism spectrum disorder (ASD), depression, anxiety, multiple sclerosis (MS), and Parkinson's disease (PD), have been associated with alterations in the mice's microbiota in several studies utilizing mouse models (PD). On the other hand, probiotics play a critical role in mending intestinal health by modifying the make-up of gut microorganisms and blocking the expansion of bad bacteria (Sharon et al. 2019; Berer et al. 2017; Cekanaviciute et al. 2017; Sampson et al. 2016).

Prebiotics are a potential substitute for the enteral injection of live bacterial species to alter the gut flora (probiotics). Non-digestible substances that feed and/or stimulate the growth of microorganisms in the colon and, in turn, boost the health of the host were coined by Gibson and Roberfroid as "prebiotics" in 1995. As described by Gibson et al. in 2004, probiotics are "selectively fermented substances that enable particular changes, both in the composition and/or activity in the gastrointestinal microbiota that imparts advantages upon host well-being and health." These components also need to be digested by mammalian enzymes and absorbed by the gastrointestinal tract without being destroyed by stomach acid. Since only a few numbers of molecules from the carbohydrate family, including fructans, Galatians, and lactulose, have been certified as prebiotics, the International Scientific Association for Probiotics and Prebiotics (ISAPP) amended this criterion in 2016.

"Compounds that may be ingested and converted by the host intestinal bacteria with the premise that they are advantageous to the host," as defined by ISAPP. The potential uses of prebiotics were broadened as a result of this definition, which allowed for the identification of new prebiotics that impact probiotic colonization and attenuate the activity of other harmful bacteria. When probiotics and prebiotics are combined, a synbiotic is produced. Prebiotics are indigestible by humans but fermentable by certain bacteria. Probiotics improve host health by altering the make-up and function of the microbiota that live in the digestive system (Gibson and Roberfroid 1995; Roberfroid et al. 2010; Gibson et al. 2017; Gibson et al. 2004).

Additionally, "psychobiotic" is used to characterize the beneficial benefits of probiotics, prebiotics, and other microbiota-targeted therapies for mental and neurological disorders (Oroojzadeh et al. 2022).

7.11 Types of Probiotics and Prebiotics

7.11.1 Probiotics

7.11.1.1 Lactobacillus

A Lactobacillus strain was among the most common probiotics, with Bifidobacterium and others close behind (Snigdha et al. 2022). Several Lactobacillus strains, especially L. rhamnosus CRL1505, have been demonstrated to reduce the severity of symptoms associated with several pediatric illnesses, including atopic dermatitis, acute gastroenteritis, and the development of necrotizing enterocolitis in babies. Protection against bacterial vaginosis and weight loss are only two of the health benefits associated with many strains of L. rhamnosus, including GR.1 and CGMCC1.3724. Taking anti-fungal probiotics like L. plantarum NRRL B-4496 and L. acidophilus ATCC-4495 may help with irritable bowel syndrome (IBS) symptoms (Fijan 2014; Sniffen et al. 2018).

The beneficial effects of L. rhamnosus LR06 on mental health include an increase in happiness and a reduction in stress, anxiety, and sadness. L. rhamnosus JB-1, on the other hand, has no effect on cognitive function (Kelly et al. 2017). Both L. reuteri ATCC and L. rhamnosus ATCC reduced the risk of neurological complications in preterm infants. In young children, the incidence of ADHD was reduced when given either L. rhamnosus GG or L. plantarum (Pärtty et al. 2015; Liu et al. 2019). L. casei (Shirota and W56) was also found to have a number of positive effects on mental health, including boosting happy mood and cognitive assessment scores, decreasing negative ruminations, boosting sad mood cognition, boosting depression assessment scores, and possibly protecting against anxiousness and fatigue (Kato-Kataoka et al. 2016; Akbari et al. 2016; Akkasheh et al. 2016; Benton et al. 2007; Chahwan et al. 2019; Mohammadi et al. 2016; Papalini et al. 2019; Smith-Ryan et al. 2019; Steenbergen et al. 2015). The immunomodulatory mechanism of L. casei Shirota suggests promise in its potential use for cancer prevention (Fijan 2014; Sniffen et al.

2018; Shida and Nomoto 2013). Minor improvements in mood, anxiety, and cognition were observed by adults who consumed lactobacillus strains such as L. acidophilus, L. helveticus, L. Preius, L. salivarius, L. plantarum, L. bulgaricus, and L. gasseri (Mohammadi et al. 2016; Romeo et al. 2011; Firmansyah et al. 2011; Marotta et al. 2019; Noorwali et al. 2017).

7.11.1.2 Bifidobacteria

Bifidobacterium bifidum, like lactobacillus, has been demonstrated to improve mental health by reducing aggression, boosting cognitive function, and reducing anxiety. Bifidobacterium longum, a probiotic bacterium, has been found to improve anxiety, tiredness, attention, mood, and sleep quality. Other species, such as lactic w19 and w58, have been shown to reduce negative thoughts, improve memory, and make people less susceptible to fatigue and stress. Other probiotics, such as the bacterium Enterococcus durans, Entorcooussu feces, and the yeast strains saccharomyces boulardi and saccharomyces servers, have also been proven to benefit host health.

Bifidobacterium species provide mental health advantages that are on par with those of lactobacillus. B. bifidum was reported to reduce aggressive thoughts, improve exam scores, and alleviate anxiety. On the other hand, it had no effect on babies' and toddlers' physical or mental growth (Akkasheh et al. 2016; Chahwan et al. 2019; Papalini et al. 2019; Smith-Ryan et al. 2019; Steenbergen et al. 2015; Noorwali et al. 2017; Bagga et al. 2019; Chou et al. 2010). Bifidobacterium longum (R0175, 1714, BL04, and NCC3001) also influences mental health by improving focus, mood, and sleep, reducing depression and psychological discomfort, and shielding the body from fatigue and worry. In contrast, Bifidobacterium longum BL999 did not influence any of the neurodevelopmental outcomes (Marotta et al. 2019; Messaoudi et al. 2011; Allen et al. 2016; Wang et al. 2019; Pinto-Sanchez et al. 2017). B. Infantis, B. animalis subsp. Lactis, and B. breve were also recognized as being major species of Bifidobacteria.

7.11.1.3 Others

The Lactococcus lactis W19 and W58 strains have been linked to improved mental health in a number of ways, including the reduction of aggressive thoughts, the strengthening of cognitive abilities in the face of artificially induced acute stress, the prevention of fatigue and anxiety, and the strengthening of the intestinal barrier (Chahwan et al. 2019; Papalini et al. 2019; Steenbergen et al. 2015; Bagga et al. 2019). Other probiotics that influence host health include Lactobacillus brevis, Lactobacillus jhonsonii, Lactobacillus fermentum, Lactobacillus acidophilus gasseri, and Lactococcus lactis subsp. lactis KLDS4.0325. Bacteria like E. durans and E. faecium (Enterococcus faecium). Streptococcus thermophilus, Pediococcus acidilactici, Leuconostoc mesenteroids, Bacillus coagulans, Bacillus subtilis, Bacillus

cereus, and Bacillus clausii subsp., O/C, N/R84, T84, Sin8), Escherichia coli Nissle 1917, F. prausnitzii, Roseburia spp., Eubacterium spp., Anaerostipes caccae, and Coprococcus spp., Anaerostipes hadrum. Using yeast strains like saccharomyces boulardi and saccharomyces cerveis has also been demonstrated to have beneficial effects on host health (Fijan 2014).

7.11.2 Prebiotics

Prebiotics are produced as a dietary supplement and may be created from a variety of different substances. Galacto-oligosaccharides (GOS), fructo-oligosaccharides (FOS), human milk oligosaccharides (HMOs), and xylo-oligosaccharides (XOS) are all examples of prebiotics that are generated from sugars (XOS). Polyphenols, phenolic acids, resistant starch, beta-glucan, inulin, stachyose, rafting, xylan, fiber gum, and Lactulose are all examples of prebiotics (Valcheva and Dieleman 2016). Polyunsaturated fatty acids (PUFA) and conjugated linoleic acid (CLA) have been labeled as prebiotics in certain research (Gibson et al. 2017). Healthy breastfed newborns had better colonization because tryptophan, lactoferrin, and HMOs may be digested by Bifidobacterium and L. acidophilus (Wala et al. 2023).

7.12 Mechanism of Action

7.12.1 Probiotics

The alteration of gut microbiota has been linked to a variety of mental illnesses. Major depressive disorder (MDD) patients were shown to have considerably lower amounts of Bifidobacteria and Lactobacilli than those without MDD (Li et al. 2014). Generalized anxiety disorder, autistic spectrum disorder, schizophrenia, and other mental disorders have all been linked to this dysbiosis (Ansari et al. 2020).

The microbiota-gut-brain axis is a proposed pathway of communication between the gut microbiota and the CNS. This interaction seems to have a beneficial effect on mental health through altering many pathways, including the modification of neurotransmitters, the anti-inflammatory activity of neurotransmitters, the attenuation of the hypothalamic-pituitary-adrenal axis (HPA), and the epigenetic process. Dopamine, serotonin, norepinephrine, and gamma-aminobutyric acid are just a few of the neurotransmitters that have been proven to rise in the presence of probiotics (GABA). In addition, some probiotics may affect the stress response controlled by the hypothalamic-pituitary-adrenal (HPA), hence influencing the levels of the hormones Cortisol and ACTH (Ansari et al. 2020; Johnson et al. 2021; Schneider et al. 2023).

By regulating the generation of antibacterial peptides like bacteriocins and improving intestinal barrier functions and permeability, probiotics may alleviate some of the symptoms of major depressive disorder (MDD) (Liu et al. 2020). When tryptophan gets severely metabolized by the indoleamine 2,3-dioxygenase (IDO) enzyme, this increases the kynurenine (KYN)/tryptophan (TRP) ratio. There is a positive correlation between KYN and the severity of depression. However, the decrease in KYN levels promotes the cognitive function of MDD patients. So, the probiotics can reduce the IDO enzyme's activity, reducing the plasma KYN level. Besides the above mechanism, L. reutari was found to have an anti-inflammatory effect by promoting the secretion of microbial histamines, thus reducing the action of proinflammatory cytokines. Also, it reduces intestinal inflammation induced by lipopolysaccharides. L. plantarum lowers the plasma KYN level and suppresses inflammation by depressing the IL-6 and TNF- α levels (Schneider et al. 2023). However, in patients with MDD treated with L. plantarum 299 V and SSRIs, a lower blood KYN level was shown to have no meaningful effect on the severity of depressive symptoms (Rudzki et al. 2019).

More importantly, probiotic neurotransmitter synthesis is related to mental health issues. When it comes to boosting neurotransmitters, Lactobacillus and Bifidobacteria shine brightest as probiotics. Dopamine, serotonin, and gamma-aminobutyric acid may all be produced by them (GABA).

Reduced levels of cortisol, nitric oxide, IL-6, TNF-, and dopamine were seen in a double-blind RCT of depressed individuals who took probiotic supplements as an adjuvant to Cipralex (SSRI) (Sevilla et al. 2021). Cipralex (escitalopram) may be to blame for the drop in dopamine levels (Dremencov et al. 2009). Both L. helveticus and B. infantis were discovered to have SSRI-like effects in an animal model. Researchers discovered that they improved serotonin and norepinephrine levels while decreasing IL-6. As a result, depressive symptoms may be reduced (Schneider et al. 2023). Despite its use as an adjunct to antipsychotic medication, probiotics did not help individuals with schizophrenia significantly (Yang et al. 2021b; Dickerson et al. 2014).

Dysbiosis has been shown to have deleterious effects on epigenetic expression. In order to repair epigenetic alterations, the gut microbiota is modulated with the help of probiotics, which generate SCFAs (Acetate, butyrate, and propionate). Anxiety was alleviated in a mouse model by administering a live probiotic, which decreased the production of IL-1, IL-6, IL-10, and TNF- mRNAs in the cortex, midbrain, and brainstem (Chan et al. 2023). In addition, B. infantis, a strong butyrate producer, showed the greatest increase in BDNF expression. Butyrate-producing probiotic F. prausnitzii possesses anti-inflammatory properties as well. When administered into a mouse model of depression, it decreased IL-6 and improved gut barrier function (Johnson et al. 2021; Chan et al. 2023). Children with autism had aberrant levels of SCFAs, Indoles, and LPS. The broken intestinal barrier might be to blame for this. Therefore, probiotics may be used to modulate gut flora and restore GI barrier function (Srikantha and Mohajeri 2019).

Another randomized controlled experiment, including the use of probiotics during pregnancy and its influence on the neurocognitive development of the offspring,

was undertaken by Slykerman et al. and followed the children for 3, 6, 12, 18 months, 2, 4, 6, and 11 years. Neither the Lactobacillus rhamnosus HN001 nor the Bifidobacterium animalis subsp. Lactis HN019 strains were shown to have any positive effects on neurocognitive or attention parameters (Tillisch et al. 2013). Another randomized controlled experiment was undertaken by Slykerman et al., who tested the effects of probiotics on the neurocognitive growth of children at 3, 6, 12, 18 months, 2, 4, 6, and 11 years of age. Neurocognitive and attention parameters are not enhanced by the HN001 and HN019 strains of Lactobacillus rhamnosus and Bifidobacterium animalis, respectively (Slykerman et al. 2018).

7.12.2 Prebiotics

Human milk oligosaccharides (HMO) containing 6′-sialyllactose or 3′-sialyllactose prevented the stress-induced loss of doublecortin (DCX) positive cells in the dentate gyrus of C57/BL6 mice (Tarr et al. 2015). Anxiolytic and anti-inflammatory effects of a galacto-oligosaccharides combination (BGOS) were found after a single injection of lipopolysaccharides into CD1 mice, decreasing IL-1 rise and inhibiting synthesis of 5-HT2AR in the prefrontal cortex, respectively (LPS) (Savignac et al. 2016). Adjunctive therapy with synbiotics has been shown to significantly reduce HAM-D in people with MDD, similar to the effects of some selective serotonin reuptake inhibitors (SSRIs). When B. longum was combined with FOS, markers of inflammation, including CRP, serum AST levels, TNF-, serum endotoxins, steatosis, and the non-alcoholic steatohepatitis activity index, were all significantly reduced (Ghorbani et al. 2018).

Some carbohydrates are metabolized by probiotics via the process of fermentation, while others are metabolized by amylase enzymes in the saliva and pancreas. Inulin and other oligo- and polysaccharides may be resistant to digestion and absorption in the upper gastrointestinal tract because they contain D-fructose connections. However, the gut microbiota ferments them in the large intestine, particularly Bifidobacteria and Lactobacillus. This results in the production of short-chain fatty acids (SCFAs) such as acetate, butyrate, and propionate, all of which have beneficial effects on the gut and, by extension, the brain through the gut-brain axis. Fecal pH is lowered, and putrefactive substances such as phenol, indole, ammonia, and branched-chain fatty acids are reduced when prebiotic meals are fermented. The “gut-brain axis” may be responsible for the effects of substrates like GOS and FOS on synaptic proteins, BDNF, and other neurotransmitters like d-serin in the brain (Valcheva and Dieleman 2016; Holscher et al. 2015; Yang et al. 2013; You et al. 2022).

7.13 Safety Consideration

Common probiotic strains are safe to use, including those from the genus Lactobacillus (acidophilus, rhamnosus, casei, plantarum, gasseri, salivarius, paracasei, and Johnson) and the genus Bifidobacterium (bifidum, longum, breve, adolescents, and animals). Some negative consequences have been linked to taking probiotics despite their many advantages. Bacteremia, endocarditis, neonatal sepsis, vaginal infections, and dental cavities are only some of the adverse reactions linked to lactobacillus strains. L. rhamnosus was linked to cases of bacteremia and systemic inflammatory response syndrome (SIRS). A female patient undergoing extensive surgery provided the most recent example (Salminen et al. 2004). The same probiotic (L. rhamnosus) was also associated with the same problem in intensive care unit patients (Yelin et al. 2019). Patients who are seriously sick or hospitalized do not benefit from probiotics, though (Sharif et al. 2022). In addition, after 4 weeks of using Lactobacillus GG, baby males with small gut syndrome developed fever and diarrhea (Land et al. 2005). Another fetus was treated with antibiotics and B. breve BBG-01 after surgery to repair an omphalocele. Blood cultures showed Bifidobacterium in the system after 2 weeks, and CRP and WBC counts rose (Ohishi et al. 2010).

Meningitis was sometimes linked to Fusobacterium necrophorum and Bacteroides fragilis (Shaheen et al. 2023a). B. brevis has also been associated with neonatal and infant meningitis (Nakazawa et al. 1996). Patients given probiotics in the PROPATRIA experiment had a higher mortality rate from acute pancreatitis. These unexpected results were subsequently attributed to insufficient technique. However, a reexamination of the data reveals that probiotics have the opposite effect and instead increase mortality via a synergistic mechanism. These routes include bacterial metabolism, host cellular failure, and pancreatic enzyme release (Bongaerts and Severijnen 2016). The overall result favored the probiotic, whether it was lactobacillus alone or in combination with Bifidobacterium, in a recent comprehensive review and meta-analysis of 24 randomized controlled trials (RCTs), including a total of 2761 newborns with NEC treated with probiotics (AlFaleh and Anabrees 2014).

Whole genome sequencing is necessary for assessing the safety of probiotics. It will help with figuring out why certain strains are harmful, tracking down antibiotic-resistant genomes, and keeping an eye out for any negative reactions to probiotics. Antibiotic-resistant genes have been found in several probiotics. In the heterofermentative strain BB-12 of Lactobacillus and Bifidobacterium animalis subsp. Lactis, for instance, the vancomycin and tetracycline resistance genes were found (Stogios and Savchenko 2020; Merenstein et al. 2023).

Companies are now facing challenges related to the dose, identity, purity, and composition of the finished probiotic product. Novel probiotic products need stringent testing and inspection to prevent contamination (Merenstein et al. 2023; Cohen 2018; Freedman et al. 2020). Freeze-dried probiotics, especially Saccharomyces boulardii, have been linked to intravenous catheter colonization, which raises

concerns about cross-contamination after the probiotics have been opened and utilized on-site (Hennequin et al. 2000).

The question of whether there is an ideal probiotic dose has been investigated in a number of studies and meta-analyses. The optimum dosage of probiotics has been the subject of several research and meta-analyses. One of them postulated that a greater probiotic dose than 5109 CFU/day might be more effective in treating AAD in children. Consensus recommendations, however, were hard to come by because of the large diversity of probiotics employed and their delivery techniques (Treven 2015). Study participants who took probiotics at a level of 1010 CFU/day had a lower chance of developing AAD. A meta-analysis reveals a wide range of dosing regimens used in human studies (Ouwehand 2017), Further, probiotics given at dosages greater than 1011 CFU/day were more effective than probiotics given at lower doses for lowering blood pressure, according to a single meta-analysis (Khalesi et al. 2014).

7.13.1 Autistic Children

The ATEC scores of autistic children decreased significantly when they were given 5 grams of powdered L. acidophilus, L. rhamnosus, and B. longum once daily for 12 weeks. Each gram of powder contained 100,106 CFUs of each strain (Autism Treatment Evaluation Checklist) (Shaaban et al. 2018).

7.13.2 Depression and Schizophrenia

Patients with mild to severe depression ($n = 110$) were randomly allocated to one of three groups: probiotics (freeze-dried L. helveticus R0052 with B. longum R0175 at a dose of 10 × 109 CFU per 5 g sachet once day before meals), prebiotics (galactooligosaccharide), or placebo (no therapy). After 8 weeks of monitoring, the probiotic group had a lower BDI score, which coincided with a drop in the ratio of KYN to TRP. In comparison to the probiotic and placebo groups, the prebiotic group showed a tendency toward a lower BDI score, although this difference was not statistically significant (Kazemi et al. 2019). The results are in line with those of a randomized controlled experiment by Wallace et al., which examined the effects of a combination of L. helveticus R0052 and B. longum R0175 administered at a dose of 3 × 109 CFU in 1.5 g sachets once daily for 8 weeks. Depressive symptoms were shown to be reduced, particularly at the mild and moderate levels (Wallace and Milev 2021). Patients were given probiotic capsules containing 6 × 109 colony-forming units (CFU) of L. acidophilus, L. casei, and B. longum once a day by Akkasheh et al. After 8 weeks, they saw a greater improvement in depression than with placebo (Akkasheh et al. 2016). For 12 weeks, patients with schizophrenia who took 8 × 109 colony-forming units (CFU) each of Lactobacillus acidophilus,

Bifidobacterium bifidum, Lactobacillus reuteri, and Lactobacillus fermentum had fewer symptoms (Ghaderi et al. 2019).

7.13.3 Healthy Geriatrics

Seniors (age 65 and above) in good health received four capsules containing 1x 109 colony-forming units (CFU) of Bifidobacterium bifidum BGN4 and Bifidobacterium longum BORI twice daily, after meals, for 12 weeks. After therapy, individuals reported decreased mental stress and unhappiness and improved cognitive performance as measured by the Korean adaptation of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD-K) (Lee et al. 2010; Bae and Cho 2004). Reducing microbiota-induced inflammations led to a rise in serum brain-derived neurotrophic factor (BDNF) compared to the placebo group (Kim et al. 2021) (Table 7.1).

Probiotics have demonstrated promising results in the treatment of a number of illnesses. Evidence on appropriate dosages for health issues other than clostridium difficile infection is currently lacking; however, the efficacy of probiotics depends on probiotic species and strains, disease specificity, the individual's Gut microbiota composition, and the method of therapy (Sniffen et al. 2018). Therefore, tailored therapies based on the microbiota are crucial.

7.14 Personalized Microbiome-Based Treatment

Gut microbiota differs from one to another due to several factors, including dietary habits (Horn et al. 2022), age (Ling et al. 2022b), genetics (Lopera-Maya et al. 2022), geographical variance (Dwiyanto et al. 2021), and physical activity (Clark and Mach 2016). The unique make-up of each patient means that even those presenting with the same clinical symptoms may have wildly diverse microbiota. These variations among people may influence how well treatment approaches work, including the use of probiotics, prebiotics, and fecal microbiota transplantation.

The makeup and activity of the gut microbiota greatly influence human metabolism, and dietary fat is a key contributor to this impact. Omega-3 fatty acids found in fish oil have been demonstrated to alleviate depression by shifting the gut microbiota away from Faecalibacterium and toward butyrate-producing bacteria (Loughman et al. 2021). The enzyme fucosyltransferase expressed by the FUT2 gene is responsible for the production of the H antigen in the intestinal mucosa and other body fluids; this antigen is a precursor to the ABO histo-blood type antigen. FUT2 secretors make up just around 20% of the population. The expression of fucosylated glycan epitopes in the human intestine is, in fact, influenced by secretor status, and the FUT2 non-secretor phenotype has been connected to variations in gut microbiota composition (Ferrer-Admetlla et al. 2009; Thorman et al. 2023). The

Table 7.1 Summary of studies investigating the psychological effects of psychobiotics

Potential psychobiotic	Dosage of psychobiotic	Observation psycho effect	Study model	Ref.
L. acidophilus, L. rhamnosus, B. longum	5 g of powder, each gram contained 100 × 106 CFUs of each strain, consumed once daily for 12 weeks	Significant improvement of autistic symptoms across ATEC scores	30 children with ASD (between 5 and 9 years old)	Shaaban et al. (2018)
L. helveticus R0052 and B. longum R0175	10 × 109 CFU per 5 g sachet once daily before meals for 8 weeks	Improvement of depression symptoms. Significant reduction in BDI scores	110 adults with MDD	Kazemi et al. (2019)
L. acidophilus, L. casei, and B. longum	6 × 109 CFU once daily for 8 weeks	Decreased depression symptoms	40 patients with MDD	Akkasheh et al. (2016)
L. acidophilus, B. bifidum, L. reuteri, and L. fermentum	8 × 109 CFU consumed every 2 weeks for 12 weeks	Alleviation of schizophrenia symptoms	60 patients with chronic schizophrenia	Ghaderi et al. (2019)
B. longum, B. bifidum, B. lactis, and L. acidophilus	18 × 109 CFU combined with 25 mg sertraline for 8 weeks	Decreased anxiety symptoms	48 patients diagnosed with GAD	Eskandarzadeh et al. (2021)
B. bifidum (Bf-688)	5 × 109 CFUs per day were administered for 8 weeks	Improvement of inattention and hyperactive/impulsive symptoms	30 children diagnosed with ADHD	Wang et al. (2022a)
B. bifidum, B. lactis, B. longum, and L. acidophilus	1.8 × 109 CFU per capsule were monitored for 2 months	No significant improvement was observed on YMRS and HADRS scales	38 patients with bipolar type 1 disorder	Eslami Shahrbabaki et al. (2020)
B. bifidum BGN4 and B. longum BORI	1 × 109 CFU per capsule per day after meals for 12 weeks	Improvement of cognitive function, mitigation of mental stress, and level of depression	63 healthy geriatrics above 64 years old	Kim et al. (2021)

L Lactobacillus, *B* Bifidobacterium, *ASD* Autism spectrum disorder, *ATEC* Autism treatment evaluation checklist, *MDD* major depressive disorder, *BDI* Benton depression inventory, *GAD* generalized anxiety disorder, *ADHD* attention deficit hyperactivity disorder, *YMRS* young mania rating scale, *HDRS* Hamilton's depression rating scale

makeup of the gut microbiota is altered by various forms of physical activity, with cardiorespiratory exercise having a greater impact than strength training (Bycura et al. 2021) (Figs. 7.4, 7.5, and 7.6).

Infusing a solution of fecal matter from a healthy donor into the intestines of a recipient with a condition related to gut dysbiosis is a profitable medical method known as fecal microbial transplantation (FMT) (Smits et al. 2013; Brandt and

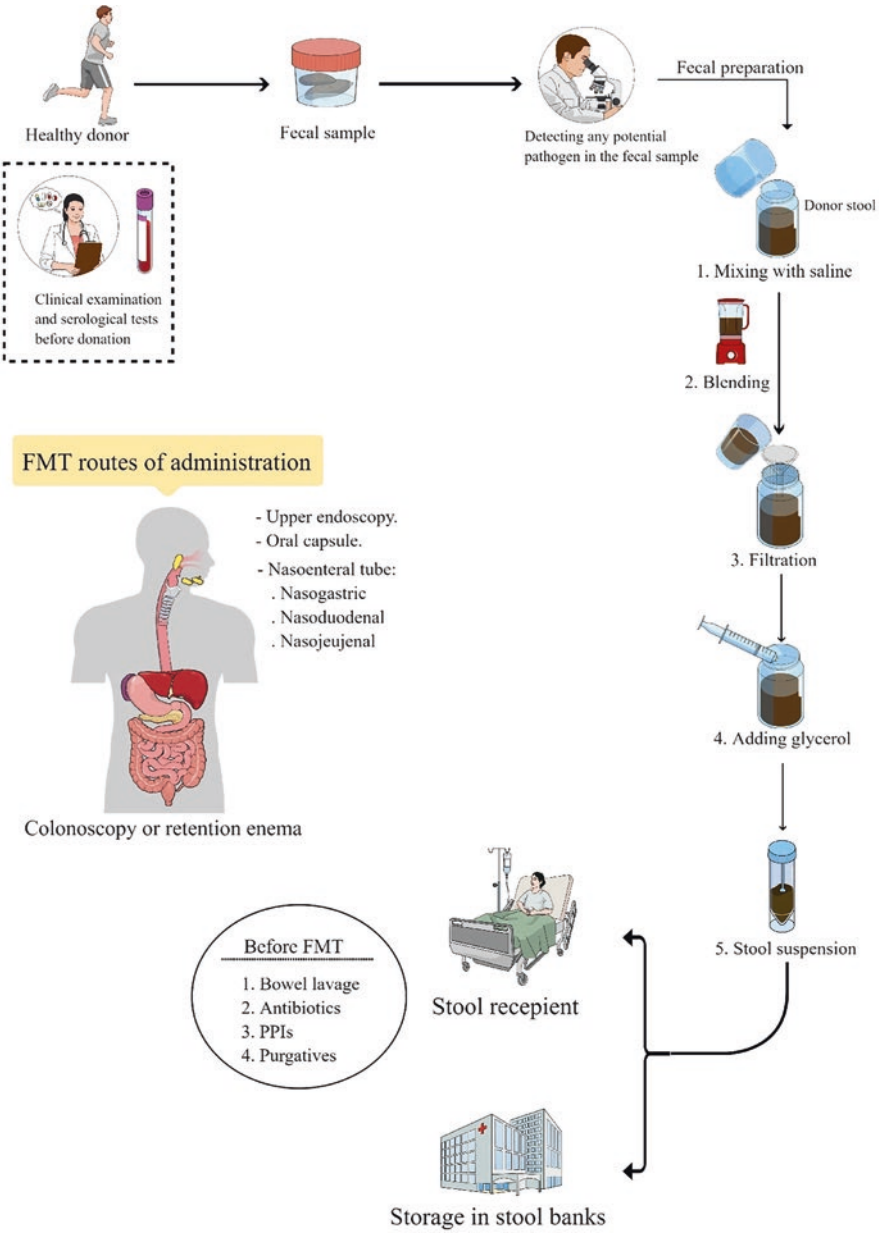

Fig. 7.4 FMT routes of administration

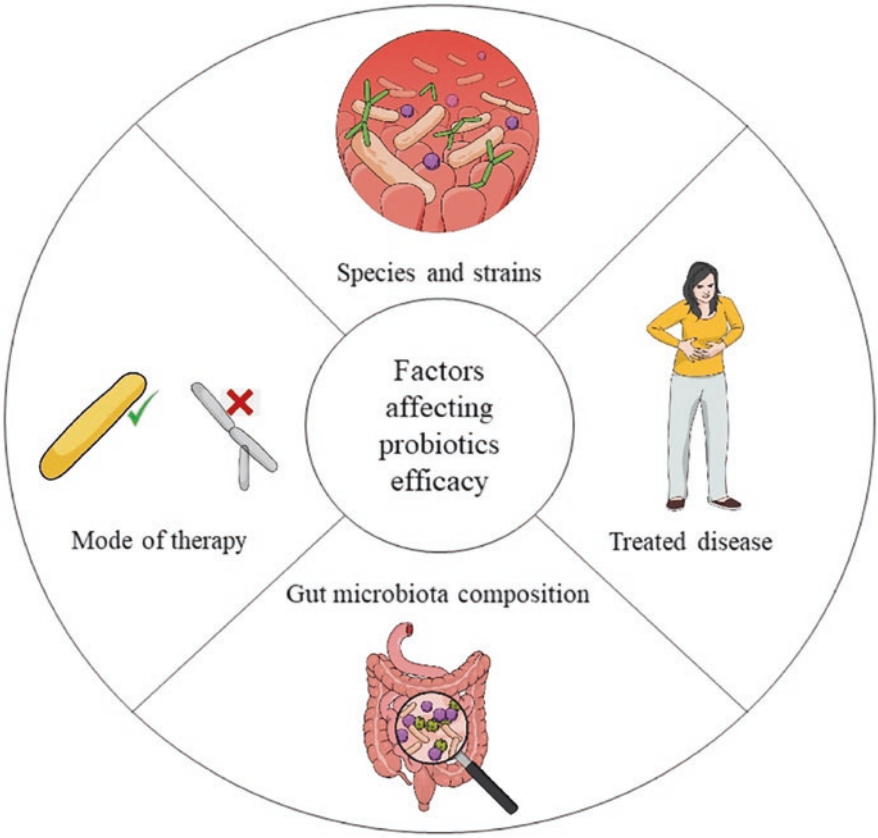

Fig. 7.5 Factors affecting probiotics efficacy

Aroniadis 2013). First-line therapy (FMT) should be considered for patients with recurrent or refractory clostridium difficile infection (CDI) if the FMT success rate is more than 90% (Kelly et al. 2021b; van Prehn et al. 2021; Lai et al. 2019). A meta-analysis of randomized controlled studies suggests that FMT may be more effective than vancomycin or placebo (Moayyedi et al. 2017). Before their blood may be used to save a patient's life, donors must undergo a series of tests (Nicco et al. 2020). The safe dose for various dysbiosis-related conditions, such as mental disorders, is yet unknown (Green et al. 2023). The most typical routes of administration are colonoscopy and enema. Despite this, it may be given by a number of potentially dangerous methods, such as capsules, a gastroenteric tube, an upper endoscopy, or a sigmoidoscopy (Kim and Gluck 2019).

Although several hypotheses have been proposed, the specific mechanism of action is still unknown. Restoring metabolic processes like SCFA and bile production and reestablishing normal gut function through the creation of a new gut composition are examples of these (Khoruts and Sadowsky 2016). Extensive testing is

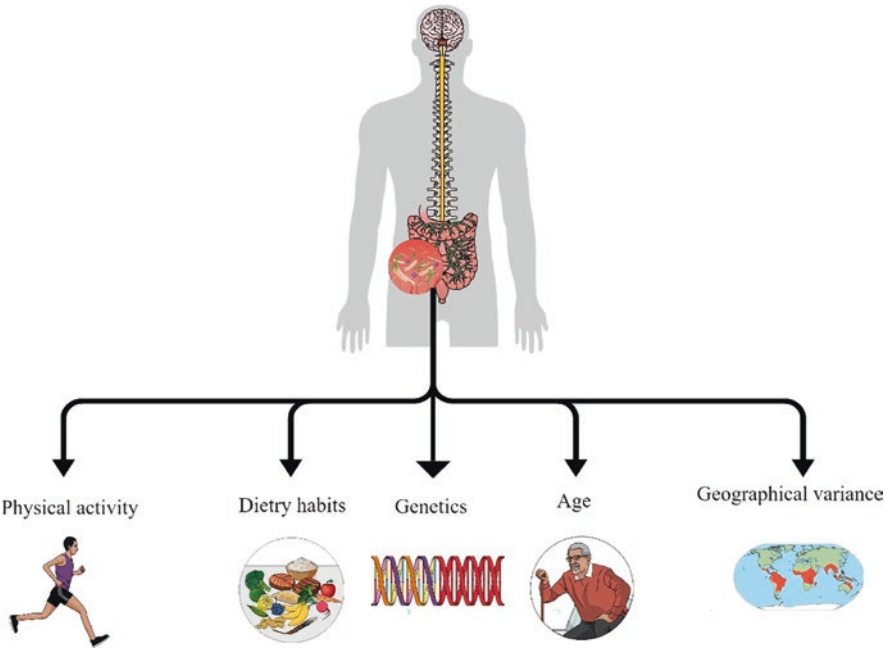

Fig. 7.6 Factors affecting gut microbiota

required of donors, including blood type analysis and stool testing for infectious illnesses. Further, a clinical and social risk assessment should be performed to rule out the possibility of a heritable gut-brain axis issue and a family history of metabolic, neoplastic, or autoimmune diseases (Bibbò et al. 2020).

Green et al. conducted pilot research to investigate the effectiveness of enema-delivered FMT for the treatment of severe depressive disorder in patients. The primary objective was to determine whether the FMT was acceptable, feasible, and safe. The exploratory result showed no significant difference between the FMT group and the placebo group when measuring the intensity of depression and anxiety, even though the FMT was well accepted, acceptable, and safe in the patients with MDD. Given the small sample size and the fact that this result was not the primary focus of the study, more large-scale randomized controlled trials are required to establish the therapeutic efficacy of the FMT in people with MDD (Green et al. 2023).

Forty children with autism spectrum disorder (ASD) were randomly assigned to receive FMT by oral (freeze-dried pill) or rectal (colonoscopy) administration, while 16 typically developing (TD) children served as a control group that received no treatment. Researchers found that ASD symptoms diminished with time. The FMT group had a 35% decrease in scores on the Childhood Autism Rating Scale after 4 weeks of intervention, as well as substantial improvement on the Autism Behavior Checklist (ABC) and the Social Responsiveness Scale (SRS) (CARS).

There is no difference between oral and rectal FMT administration for symptom relief in ASD (Li et al. 2021b). These results backed up the claims of Kang et al., who expected that children with ASD would see a decrease in ASD-related symptoms after FMT and that this improvement would endure for at least 8 weeks (Kang et al. 2019).

However, there is a dearth of data on how FMT influences dysbiosis-related mental diseases. The underlying process has to be explored in more depth. Large, double-blind, randomized clinical trials of FMT are required to determine its therapeutic efficacy and to identify any serious mental health risks associated with it. All donated feces must be extensively tested due to the potential for the transmission of multidrug-resistant pathogens, resulting in serious illnesses, particularly in immunocompromised patients. Because of the potential for FMT to transmit monkeypox in healthcare settings, the FDA has issued a warning (Food and Drug Administration 2022; Owais and Iqbal 2022). The role of FMT in pregnant women and others with impaired immune systems is similarly little understood. Therefore, probiotic distribution should be tailored to each person, and we need to abandon the "one size fits all" approach to prescription in the near future (Stefanicka-Wojtas and Kurpas 2023) (Figs. 7.4 and 7.5).

7.15 Novel Psychobiotics

Psychobiotics include, for example, substances that improve mental health, such as probiotics, prebiotics, and synbiotics. Mood disorders, including depression, anxiety, schizophrenia, autism, and ADD/ADHD, have all been demonstrated to respond well to psychobiotic treatment. However, new research has looked at how "psychobiotics" affect people's brains.

Recent studies have shown that several probiotic strains, including Lactobacillus acidophilus ATCC 4356, Lactobacillus gasseri ATCC 33323, Lacticaseibacillus rhamnosus GG ATCC 53103, and Lactobacillus plantarum GXL94, have antioxidant activity in vitro (Vougiouklaki et al. 2023; Zhou et al. 2022) Bifidobacterium longum subsp. Infantis BF17–4, B. bifidum BF88–5, and BF87–11 were more effective in quelling hydroxyl radicals than Lactobacillus rhamnosus GG. Bifidobacterium longum strains T27a and BL-10, as well as Lactobacillus plantarum NJAU-01, have shown antioxidant activity in preliminary studies (Wang et al. 2023a; Ge et al. 2021). The probiotic supplement Lactobacillus fermentum ME-3, on the other hand, has been shown to fully activate the glutathione system, in addition to having antibacterial and antioxidative effects (Mikelsaar and Zilmer 2009; Pelton 2022). A recent meta-analysis of 52 RCTs found that those who took antioxidant supplements had significantly lower levels of depression and anxiety. The fundamental mechanism is poorly understood (Wang et al. 2023b). Therefore, the antioxidant effects of these probiotics may have a positive impact on mental health.

In recent studies, Zhu et al. worked with sixty nervous first-year college students. The probiotic (Lactobacillus plantarum JYLP-326) or a placebo was given to participants at random. Thirty students who did not experience anxiety were enrolled as a control group. One gram of freeze-dried L. plantarum JYLP-326 was given to the probiotic group twice a day for 3 weeks prior to the final exams. After the intervention was over and during the test time, the HAMA-14, HDRS-17, and AIS-8 were used to evaluate anxiety, depression, and drowsiness, respectively. The study participants who took probiotics reported significantly lower levels of anxiety, depression, and insomnia compared to the control group. They also found that the intervention had rearranged the fecal microbiome. In conclusion, Lactobacillus plantarum JYLP-326 protects college students from stress-induced dysbiosis by decreasing physiological anxiety, melancholy, and insomnia and enhancing fecal metabolic rearrangement (Zhu et al. 2023).

According to the research of Satoh et al., xenobiotics represent a novel class of prebiotics. He demonstrates the unique prebiotic based on ketone body metabolism. Ketone (3-hydroxybutyrate) donation induces "exogenous ketosis," which is better than "endogenous ketosis," which requires severe dietary restriction to stimulate ketone body metabolism by cells due to a lack of glucose. He demonstrates that when poly-hydroxybutyrate (PHB) is administered to the large intestine and hydrolyzed by depolymerase, a significant amount of 3-hydroxybutyrate (3HB) may be digested by the gut bacteria. Afterward, the microbiota produces SCFAs, which activate regulatory T cells, which subsequently circulate throughout the body, influencing a wide variety of tissues and organs, such as the brain and the skeletal muscles (Satoh 2023).

Synbiotics are a novel category of supplements made by mixing probiotics and nonoprebiotics. The effectiveness of a synbiotic product, including the probiotic Lactobacillus plantarum and the prebiotics pullulan and phthalyl pullulan nanoparticles, was investigated by Hong et al. using an antibiotic-induced dysbiosis mouse model. They used the dangerous strain of E. coli K99 to evaluate the synbiotic. An intriguing discovery was that the pathogenic effect of E. coli k99 was reduced, the gut microbiota was restored, and the diversity and richness of the gut microbiota were both enhanced. The improved intestinal permeability and strengthened intestinal barrier led to a decrease in endotoxemia. The study found increased populations of Bifidobacterium, Lactobacillus, and LAB (Hong et al. 2021).

7.16 Long-Term Manipulation of Microbiota

Although probiotics have been shown to help repair and manage the gut microbial community and population, it is still unknown whether or not taking such supplements on a regular basis would have a positive effect on a wide range of ailments (Wiegers et al. 2022). However, new ideas and studies are starting to emerge. The delicate balance essential for good health is threatened by probiotics, which are

considered to alter the beneficial local microbiota. This raises concerns about long-term colonization (Merenstein et al. 2023) (Figs. 7.4, 7.5, and 7.6).

Hradick et al. administered lactobacillus plantarum VD23, L. plantarum C28, L. plantarum MS18, Ligilactobacillus salivarius MS3, MS6, and MS16 to 8 male Wister rats and a placebo to 8 male Wister rats. Probiotic supplementation had no effect on the general health of the rats after 8 months of therapy. TNF-alpha, interleukin-1, and interferon-alpha were all upregulated, however, indicating an inflammatory response. The fecal flora was altered, and there were more lymphoid aggregates in the colon. These findings raise the possibility that long-term probiotic usage in humans is associated with a more gradual deterioration in health under specific conditions (Hradicka et al. 2023).

Rahimlou et al. randomly assigned 70 MS patients to either receive probiotics or a placebo. Both the Beck Depression Inventory-II (BDI-II) and the General Health Questionnaire-28 (GHQ-28) were used to assess psychological health (GHQ-28). Probiotics group participants got two capsules daily with a 1 × 1010 CFU/gram probiotic dosage for a total of 6 months. Each tablet included 14 unique types of microorganisms. During the course of the experiment, both depression symptoms (as evaluated by the BDI-II) and distress (as measured by the GHQ-28) improved in the treatment group when compared to the placebo group (Rahimlou et al. 2022).

In another randomized study, Wang et al. looked at 79 people with a diagnosis of temporal lobe epilepsy (TLE). The Hamilton Depression Scale (HAMD), the Hamilton Anxiety Rating Scale (HAMA), the Wechsler Adult Intelligence Scale—Fourth Edition (WALS-IV), and the Wechsler Memory Scale—Fourth Edition were used to assess the individuals' mental health (WMS-IV). The Hamilton Depression and Anxiety Scale showed that after 3 months of follow-up, the probiotics group had significantly less depressive and anxious symptoms than the placebo group. On the other hand, no significant difference was seen between the probiotic and placebo groups using the WMA or WALS-IV scales (Wang et al. 2022b).

7.17 Ethical Consideration

Despite the growing number of studies dedicated to the microbiome, little has been said about microbiome ethics. There are few scholarly writings that deal with this issue. Both the donor and the recipient must be made aware of the risks and rewards, as well as the standards and procedures for ensuring quality in the feces donation process. It is equally as important as the other four principles of clinical ethics (beneficence, non-maleficence, autonomy, and fairness) (Rhodes 2016; Lange et al. 2022; Tuomola et al. 2001; Harrison et al. 2015; Jahn 2011).

The usage of FMT is discouraged outside of the classroom. It may be the last resort of the treating physician when all other conventional treatments have failed or when no other therapeutic choices are available. With the approval of an ethical committee and the patient's informed consent, FMT may be used compassionately. Many unanswered problems remain about the use of FMT in contexts other than

CDI. Among these challenges include making sure FMT is properly incorporated into treatment and finding compelling donor profiles for each indication (Cammarota et al. 2019). The identity (including the patient's behavior and feelings) and fertility of the recipient may be affected by a transgender feces transplant. Furthermore, friendship and mutual trust (FMT) are linked (Metselaar and Widdershoven 2017).

7.18 Conclusion

The gut microbiota has a substantial effect on human health, influencing everything from immunity and digestion to mental health. Its composition is controlled by genetics, nutrition, and environment, and dysbiosis plays a role in obesity, diabetes, and mental health concerns, among others. The neurological, hormonal, immunological, and metabolic processes that comprise the bidirectional gut-brain axis serve as a communication network between the gut and the brain. This intricate connection influences mental health, behavior, and emotion. Targeting the gut microbiota with probiotics and prebiotics has the potential to cure metabolic and mental health disorders. To completely comprehend its intricacy and develop effective solutions, further study is required. Although individualized approaches, optimal doses, and ethical issues must be considered, the emerging field of psychobiotics has promise for treating mental health disorders. Although individualized methodologies, appropriate doses, and ethical implications must be thoroughly investigated, the emerging field of psychobiotics has promise for the treatment of mental health issues.

7.19 Recommendation

As our understanding of the gut-brain axis continues to expand, future research should concentrate on a number of crucial areas to better comprehend the intricate relationship between gut microbiota and mental health. It is required to undertake longitudinal studies to determine the long-term effectiveness and safety of psychobiotic therapy and to assess their long-term impacts. Studying the benefits of personalized treatment, such as FMT tailored to individual microbiome profiles, is an additional intriguing field for focused mental health care. Ethical issues should remain at the forefront of research design and execution to ensure patient confidentiality, informed consent, and the responsible use of innovative medications (Shaheen et al. 2023b). Lastly, a study into contemporary psychobiotic treatments, such as antioxidants, xenobiotics, and synbiotics, may provide fresh light on cutting-edge techniques for promoting mental health. Collaboration between researchers, doctors, and ethical committees will be vital as the field evolves to guide future research and find effective treatments for mental health disorders.

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Chapter 8
Toward Better Science-Based Advice on Nutrition

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Abstract Does our diet have an impact on how we feel mentally? A growing amount of evidence indicates that nutrition and dietary requirements are essential for body composition and human physiological development, which also significantly influences attitude and mental wellness. A bad diet is significantly linked to mood conditions escalation, for example, depression and anxiety, like other neurological diseases, regardless of the factors influencing psychological wellness are complex. There are widespread assumptions concerning the health risks of specific meals that are not backed by trustworthy data. Additionally, there is currently a lack of strong scientific data linking nutrition to mental health. The most recent epidemiological evidence linking diet to mental health does. There is currently no knowledge of causality or underlying processes in the epidemiological data on nutrition and mental health. The goal of future research should be to clarify mechanisms. Researchers explore the empirical data demonstrating the significant benefits of a whole diet for mental health and present an introduction to the developing subject of nutritional psychiatry. This book chapter provides a mechanistic understanding of the subject, an experimental medicine approach, and data required to support future dietary and nutritional policies for mental well-being.

Keywords Mental health · Neurological illnesses · Nutritional psychiatry · Nutrients · Ketogenic diet

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Abbreviations

AD	Alzheimer's disease
AHAD	American Heart Association Diet
AHEI	Alternative healthy eating index
BMI	Body mass index
CRP	C-reactive protein
CSF	Cerebrospinal fluid
DASH	Dietary approach to stop hypertension
F/B	Firmicutes/Bacteroidetes
GI	Glycemic index
IL-6	Interleukin-6
KD	Ketogenic diet
MI	Myocardial in fraction
MMKD	Modified mediterranean-KD
p-tau	Phosphorylated tau
RCT	Randomized controlled trials
SCFAs	Short-chain fatty acids
VLCKDs	Very-low-calorie ketogenic diets

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8.1 Introduction

Diet and mental health are related, as shown by epidemiological research and the results of intervention trials. Additionally, following specific diets is beneficial for people with known hereditary and nongenetic ill, for example, phenylketonuria, gluten sensitivity, and lactose intolerance. Even still, a lot of relationships are debatable, and it's quite challenging to find solid proof of a causal mechanism. Little is known about the precise dietary elements that support a person's mental health. This study vacuum must be bridged to have good dietary recommendations evidence based on the equilibrium of the mind (Jacka et al. 2017; Marx et al. 2017; Sarris et al. 2015a, b).

There are several obstacles to be overcome there are many understanding of how nutrition influences metabolism in the gut, including microbiota, how this affects gut-brain signals, how nutrition impacts blood levels of metabolite and tissues of targets, particularly via hormones of the gut, blood levels of metabolite and target organs as a result of food, Diets utilized for mental health must take into account how genetic background affects and how diet affects mental health for people's. Knowing the physiological and metabolic mechanisms of how nutrition might increase neurons' resistance to injury and enhance mental fitness will aid in deciding how to modify food composition most effectively. New hypotheses should be developed and tested with experimental medical techniques using the data acquired from such cohorts Fig. 8.1 (Adan et al. 2019).

Experimental medicine studies link preclinical mechanisms research to clinical trials. They also use laboratory-based experimental design to ensure rigor and well-defined results (Dawson et al. 2011). Individual eating habits and eating patterns, regardless of depression, affect total food consumption and quality of diet (Paans et al. 2019), which should also be considered.

8.2 The Paucity of Empirical Evidence Supporting Eating Effects on Mental Health

8.2.1 Compliance with Dietary Advice and Depression Risk

Numerous research that looked at various groups depending on origin, age, and gender found that high dietary adherence had an important protective impact against depression and depression symptoms (Adjibade et al. 2018; Akbaraly et al. 2013; Collin et al. 2016; Emerson and Carbert 2019; Huddy et al. 2016; Jacka et al. 2017; Ruusunen et al. 2014). In Australia, high dietary adherence was linked to a considerably lower chance of first-time moms experiencing depression symptoms (Huddy et al. 2016). In France, adults with high dietary adherence Have a lower chance of acquiring symptoms of depression (Adjibade et al. 2018).

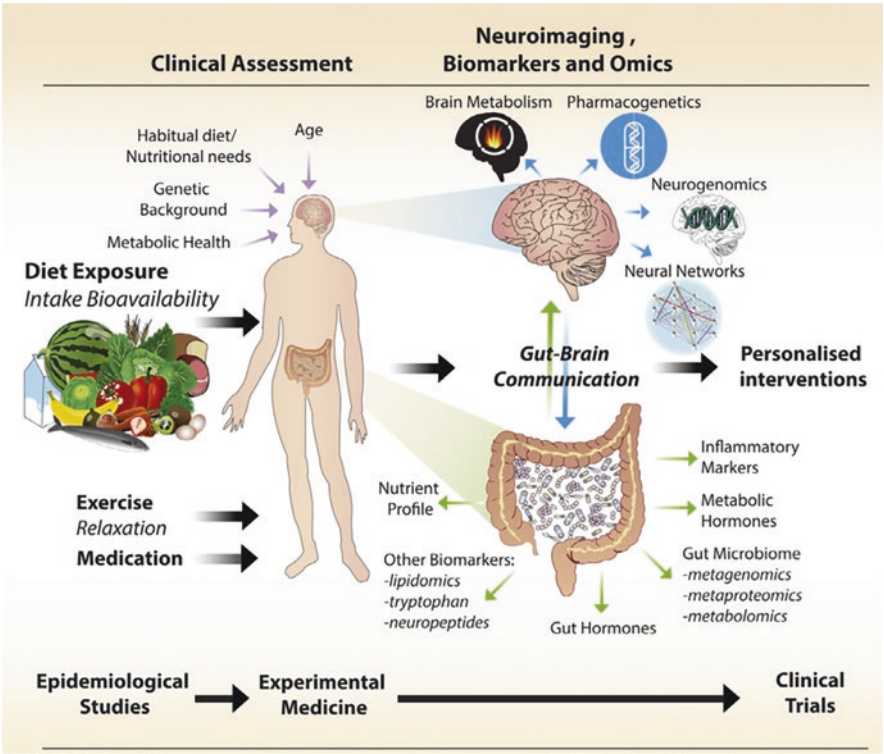

Fig. 8.1 The integrated study of nutritional intervention, and care, for emotional disorders treatment. (Adapted with permission from Ref. (Adan et al. 2019) Copyright 2023, Springer nature)

In this study, risk reduction was assessed to be 21%, 20%, and 12%, respectively, and no significance was found for the group AHEI-2010. A high level of French adherence to nutrition and exercise guidelines was linked, in a highly significant way, to a lower incidence of depression (Collin et al. 2016). The following dietary guidelines can help older adults and middle-aged with a previous or current depression diagnosis achieve greater mental health (Elstgeest et al. 2019). The relationship between failing to abide by the Alternative Healthy Eating Index (AHEI) and a Mediterranean diet. A considerably increased depression risk was evident only among men. Abide by the Dietary Approach to Stop Hypertension (DASH) diet did not significantly correlate with depression, according to research (Elstgeest et al. 2019).

AHEI has demonstrated a strong correlation with female depression prevention benefits (Akbaraly et al. 2013). In a similar study, greater intake of fiber, vegetables, and fruits, as well as lower consumption of trans fats, was linked to a lower occurrence of depressive disorders. AHEI research revealed dietary recommendations with a significant female dose response. Over a 10 year period, Higher AHEI scores in women were associated with a 65% reduction in the likelihood of recurrent

depression than women with lower AHEI scores. In the study, men did not show any significant outcomes (Akbaraly et al. 2013).

A healthy diet is abundant in vegetables, fruit, chicken, fish, legumes, low-fat cheese, whole grain products, and berries was contrasted with the standard Western diet rich in processed foods such as fast foods, French fries, sausages, sweets, for example, cakes, candy, ice cream, chocolate, baked potatoes, processed meat, eggs, and high-fat cheese in a study in Finland (Ruusunen et al. 2014). Greater healthy adherence to the eating regimen was found to have a significant protective impact in the examined men in their middle age in Finland. The shielding impact was calculated as a 25% lower probability of experiencing depressed symptoms. In the same study, a 41% rise in the probability of depressive symptoms was found to be significantly higher with a Western diet. A balanced diet and consumption of vegetables and fruits have been shown to significantly benefit Canadian immigrants' mental conditions, and eating more vegetables and fruits was linked to a 19–23% improvement in mental wellness (Emerson and Carbert 2019).

8.2.2 Depression and Pro-inflammatory Diet

Numerous research has proved a link between a high-fat diet in inflammatory potential and the likelihood of depression in various groups of people (Adjibade et al. 2017, 2019a, b; Bergmans and Malecki 2017; Chang et al. 2016). Whole grains, fish, vegetables, and olive oil have been demonstrated to have a lower influence on systemic inflammation. Refined wheat, Sweets, red meat, High-fat diets, processed meat, and other products had a greater impact on chronic inflammation in the body, according to the research (Adjibade et al. 2019b). The results showed that middle-aged adults, overweight and obese people, and women had much higher rates of depression than those who had a diet that promoted inflammation. Therefore, individuals who were overweight or obese had a higher connection (Adjibade et al. 2019b).

The findings demonstrated a diet that promotes inflammation was connected to a considerably higher depression prevalence in adults of middle age, overweight and obese individuals, and women. The association was therefore stronger in those who were overweight or obese (Adjibade et al. 2017, 2019a, b). Consuming a diet higher in pro-inflammation foods significantly enhanced the likelihood of depression symptoms in specific male groups who smoked and were sedentary bodily (Adjibade et al. 2017; Bergmans and Malecki 2017). An American cross-sectional research study found that associations between foods with an effect of inflammation and an elevated depression risk were computed Statistics with significance (Bergmans and Malecki 2017). In the same research, the existence of ongoing anxiety was highly related to a significant inflammatory food consumption. Another American research found a substantial link between eating an inflammatory diet and a woman's chance of developing depression (Lucas et al. 2014).

8.2.3 Depression and Dietary Micronutrient Intake

An increased mental disease risk has been linked to nutritional micronutrients (Adjibade et al. 2018, 2019b; Chang et al. 2016; Godos et al. 2018; Gougeon et al. 2016; Lai et al. 2016; Yary et al. 2016). Magnesium consumption through food was strongly linked to middle-aged men's depression risk (Yary et al. 2016). The amount of magnesium in the diet was calculated using three statistical models, and the least amount of magnesium consumed was related to a significantly increased depression risk. Comparing the three study models, it was exposed that individuals who consumed the most magnesium had a strategy for avoiding depression (Yary et al. 2016).

Interactions between magnesium, folic acid, and B12 intake were revealed as unintended consequences in the study's findings, which focused primarily on whether or not people followed healthy dietary recommendations (Adjibade et al. 2018). In a similar study, those who most strictly followed the guidelines for a healthy diet showed lower rates of symptoms of depression and significantly higher intake of nutrients such as folic acid, calcium and magnesium, B12. Another study discovered that people who consumed the most processed foods had a higher risk of developing depression and consumed less magnesium, B12 vitamins, and folic acid in their diets than those who consumed the fewest processed foods (Adjibade et al. 2019a). Depression risk and vitamin B consumption have been calculated to have significant relationships in both sexes (Gougeon et al. 2016). The highest B6 consumption in women was linked to a decreased risk, whereas the highest B12 intake in men was related to a reduced risk.

Low levels of vitamin B12 and B6 as well. Have been shown to increase the chance of getting depression in a related study. Consumption of fatty acids was investigated as a possible moderator of inflammatory risk and associations with depressive disorders in elderly people (Lai et al. 2016). C-reactive protein (CRP) and interleukin-6 (IL-6) were utilized in the study to assess inflammatory markers. The findings, which showed that polyunsaturated fatty acids and omega 3 were protective in males with depression, had a significant impact on CRP.

Moreover, intake of total fat, saturated fat, and monounsaturated fat had a substantial impact on the levels of CRP and IL-6 in women. In one research, flavonoid subclasses that were ingested by food dramatically decreased the likelihood of female depression. The top consumption of flavones, flavanones, and flavones was also pointedly connected to a 7–10% decreased incidence of depression compared to the least amount consumed, According to a USA study (Chang et al. 2016). Depression symptoms were compared with food consumption of total polyphenols, classes, and subclasses, and substances in a Godos et al. study (Godos et al. 2018). No significant correlation between the overall consumption of polyphenols and depressed symptoms was discovered in their findings. This study evaluated the significance in subclasses and found that higher flavonoid consumption may be negatively correlated with depressed symptoms.

8.2.4 Dietary Preference and Depression Risk

The depression risk has been linked to certain diets (Adjibade et al. 2019a, b; Gangwisch et al. 2015; Matta et al. 2018; Smith et al. 2014). Certain foods have been related to an increase in depression risk when they are removed from a person's diet, according to research (Matta et al. 2018). The occurrence of depressed symptoms was highest (28.4%) among vegetarians while eating meat had the lowest (16.2%). According to the findings, With each food being ignored, the likelihood of experiencing depression grew dramatically and independent of diet (Matta et al. 2018). Young women showed a dose-response association between eating fish and their chance of experiencing depression was reduced by 6% for each fish serving (Smith et al. 2014). Comparing women who ate fish more frequently to those who ate it less frequently, those who ate fish at least twice a week had a 25% decreased incidence of depression. However, women who did not experience depression were 15% less likely to eat fish twice a week. There was no link found between eating fish and male depression (Smith et al. 2014).

In one study, which looked at a pro-inflammation diet and the risk of depressive symptoms in both women and men, fish consumption was considered a variable (Adjibade et al. 2019b). There was a considerably higher depressive symptom risk with a high diet of pro-inflammation foods. Additionally, compared to individuals with the highest risk of contracting the condition, men and women who ate a more natural diet had considerably lower intakes of fish, eggs, and meat (Adjibade et al. 2019b). In the USA, postmenopausal women were shown to have a considerably higher risk of depression when their diet's glycemic index (GI) was high (Gangwisch et al. 2015). High intakes of vegetables, fibers, and fruits were connected to a significantly decreased incidence of depression in the same study, while larger intakes of added sugar were linked to a significantly higher risk of the condition. In comparison to traditional treatment (social support group), personal counseling combined with motivational interviewing (MI) boosted maintaining a nutritious diet (Jacka et al. 2017).

8.2.5 A Correlation Between Depression and Diet

Two randomized controlled trials (RCT) studies were among the findings, and they allowed us to establish a link between food and mental disease (Jacka et al. 2017; Parletta et al. 2019). According to social conversation support and MI, counseling sessions lasted a similar amount of time in both groups. The number needed to treat (NNT) 4 was used to determine the severity of the finding, and people who received assistance for dietary adjustments as a result of MI displayed noticeably decreased depressive symptoms (Jacka et al. 2017). People with depression experienced

significant improvements in their mental health when they adopted a Mediterranean diet (Parletta et al. 2019). The group receiving the intervention that received support and group guidance for adhering to the Mediterranean diet ingested significantly more fruits, vegetables, and whole grains than the control group (Parletta et al. 2019). Contrary to the control group, which did not receive encouragement or group instruction in consuming in accordance with the Mediterranean diet, the intervention group participated in group meetings with social activities and consumed significantly more whole grains, vegetables, fruits, and nuts as well as pointedly little sugar. A 1.68-fold decline in symptoms of depression was assessed in the diet intervention group, and this reduction persisted over the course of the 6-month follow-up (Parletta et al. 2019).

The results of this study showed that nutrition can help to prevent and treat mental illnesses. High dietary adhesion, eating fish, following an anti-inflammatory diet, and avoiding processed foods have all been associated with a lower prevalence of mental illness and an appropriate intake of various fatty acids, magnesium, and folic acid. Following dietary recommendations results in a sufficient intake of nutrients, which lowers the chance of developing mental illness and lessens its symptoms. In diverse age groups and populations, the study's findings indicated a dose-response link between adhering to dietary advice and a decreased risk of mental illness. The result is consistent with earlier research that has revealed that a diet rich in fruits, fish, and vegetables can reduce the risk of depression, while a diet high in junk food, soda, and added sugar was linked to a higher depression risk (Huang et al. 2019b; Nicolaou et al. 2020).

This study's findings, together with different new studies, support the recommendations made by Berk et al. It is advisable to follow dietary guidelines provided by experts and the World Health Organization (WHO) as They have been demonstrated to be protective against mental disease (Nicolaou et al. 2020). Anti-inflammatory foods help alleviate symptoms and protect against mental illness. Food may affect the body's inflammatory response and be associated with higher depression risk. This study has shown that a diet low in pro-inflammation foods decreases depression risk and its indications, whereas a diet strong in pro-inflammation foods increases the risk. In other countries, researchers have found that eating a lot of foods that can cause inflammation in our bodies is connected to feeling sad and worried (Salari-Moghaddam et al. 2019).

In an additional study, adolescent girls' propensity for inflammation was investigated, and The outcomes revealed that the girls' levels of stress were significantly higher when their diets contained a high proportion of pro-inflammatory items (Lassale et al. 2019; Shivappa et al. 2017). In additional research, adolescent girls' propensity for inflammation was investigated; a study found that when girls ate a lot of foods that can make their bodies feel stressed, it made them feel even more pro-inflammatory symptoms (Peirce and Alviña 2019). The findings demonstrated that probiotics and prebiotics, which are foods for healthy bacteria, improve digestive health, which can lessen inflammation and the symptoms of mental illness (Peirce and Alviña 2019). To prevent and treat mental disease, foods that cause inflammation should be avoided.

The numerous dietary micronutrient constituents can be quite important for the treatment of depression. Dietary fatty acids have been linked to a higher likelihood of developing depressive symptoms and can affect the body's level of inflammation. In this research, micronutrient intake provided a defense against depressive symptoms. Increased dietary intakes of magnesium, vitamin B6, vitamin B12, folic acid, and other nutrients showed protective effects against mental symptoms in various groups. The fatty acid composition of the diet was essential for mental illnesses due to increased inflammation, and particular fatty acids either enhanced or lowered the chance of depression.

The study's outcomes are corroborated by research on older adults, wherein both sexes, low serum levels of folate and B12 were linked to increased depression risk (Petridou et al. 2016), and high nutritional B6 and B12 consumption were associated with an important protecting effect against the depression onset (Skarupski et al. 2010). Other research has revealed that groups of individuals of all ages who consume inadequate amounts of magnesium have increased risks of depression (Tarleton and Littenberg 2015). A meta-analysis of previous research found a significant correlation between folic acid concentrations and depression (Bender et al. 2017; McEligot et al. 2018). Low blood levels were connected to a higher depression risk, but high food intake was linked to a protective effect against depression.

All ages should be encouraged to eat a diet with sufficient micronutrients because It may aid in preventing depression. Consumption of processed meals with a high GI, for example, whole foods, sweets, and soft drinks, as well as dietary exclusion from the food, may be linked to an elevated risk of mental disorders. Eating a lot of sweets and other high GI foods was connected to Other healthy food options, like greater consumption of fish and a diet rich in Mediterranean foods, which may have a protective impact against depression and depressed symptoms. Additionally, the amount of foods cut out of the diet increased the incidence of depression regardless of diet. According to numerous studies and meta-analyses, persons who ate Western food had a much higher depression risk development than those who consumed a lot of whole grains and vegetables (Li et al. 2017). Another study of the literature looked into the relationship between the intake of Soft drinks with added sugar and the chance of developing depression. The findings indicated that those who consume a lot of soft drinks have a much higher risk of depression. According to various studies (Yang et al. 2018), eating fish lowers the chance of developing depression. Yang, Kim, and Je discovered a substantial dosage response association in the most recent publication of these reviews, which supports the findings of the current investigation. Fish and a varied diet high in unprocessed foods can help avoid depression (Yang et al. 2018).

Dietary changes would be a successful treatment of depression. A reduction in depression symptoms can be achieved through myocardial infarction (MI) and group interventions that include education and guidance on nutritious eating.

Body Levels of inflammation have been linked to numerous sickness states, including mental illness (Adjibade et al. 2017, 2019a, b; Bergmans and Malecki 2017; Lucas et al. 2014). The metabolic syndrome has a significant global prevalence (about one trillion individuals), and prediabetes, high blood pressure, and

increased inflammation are the results (Saklayen 2018). This connection makes sense, given that everything is linked and that mental and physical health cannot be separated. When the root reason is harmful living practices, a huge portion of today's mental disease can be avoided. Healthcare practitioners must work more preventively and treat causes as opposed to symptoms. The conclusions of the present investigation are strengthened by the presence of RCT trials and excellent quality cohort research with solid evidence.

Based on the knowledge derived from the findings of the most current reviews, the creation of the dietary recommendations proposed by Berk et al. (Nicolaou et al. 2020) may be decided. Additionally, this information can be utilized by public health experts in their work to promote health, preferably in combination with MI at both individual and group levels. There are few RCT studies using nutritional counseling treatments to urge and motivate people to change their eating habits, but those that do exist have shown a positive effect.

To better understand how to help people change their eating habits for the mitigation and treatment of feeling depressed or symptoms of depression, more research is required.

8.3 Ketogenic Diet

Dr. Russel Wilder first proposed the ketogenic diet (KD) in 1921. The KD is described as having moderate protein, low carbohydrates, and high fat (Sampaio 2016). The traditional KD is based on a 4:1 ratio of lipids to a mix of carbohydrates and proteins, which is the industry standard (Sampaio, 2016; Wang et al. 2021). Protein and carbohydrates only provide 6% and 4% of the calories in this diet plan, respectively, while fat makes up 90% of the calories. Before antiepileptic drugs were first available in 1938, this dietary approach to treating epilepsy was widely utilized (Sampaio 2016). To meet the various lifestyles, numerous less restrictive (KDs) with Variable ratios of fat, protein, and carbohydrates have been created, including a modified Atkins diet, medium-chain triglyceride diet, and low glycemic index treatment (Miranda et al. 2012).

8.3.1 Therapeutic Application of Ketogenic Diet

8.3.1.1 Epilepsy

In a blinded, controlled study carried out by Neal et al. (2008), it was shown that KD is effective in treating childhood epilepsy. Three months following diet intervention, there was a clinically significant reduction of 75% in the mean proportion of baseline seizures between the 54 epileptic children assigned to the KD group and the 49 epileptic children in the control group. Adults have also shown that KD is helpful; a

study including 23 epileptics found that 39% of them attained a 50% reduction in seizure frequency, while 22% of them showed a 50% drop or inconsistently a 50% decrease (Schoeler et al. 2014).

Meanwhile, in 1916, Dr. Charles Reed connected Bacillus epilepticus and epilepsy to constipation, which marked the beginning of the gut microbiota and epilepsy theory (Reed 1916). Given the availability of cutting-edge genetic technology, researchers started investigating the gut microbiome of the patients and its potential relationship with the pathophysiology of epilepsy. In line with this, Xie and his colleagues discovered that newborns with refractory epilepsy had larger proportions of Proteobacteria and lower proportions of Actinobacteria and Bacteroidetes. However, the Firmicutes bacterial community predominated in the cohort of newborns with epilepsy. Additionally, babies with epilepsy have less diversity in their gut microbiome (Xie et al. 2017). In addition, Peng et al. found that the drug-resistant epilepsy group had a lower amount of Bacteroidetes than the drug-sensitive plus healthy people had and that Firmicutes and Verrucomicrobia were more prevalent.

Dorea, Atopobium, Saccharibacteria, Coprobacillus, Delftia, Clostridium XVIII, and other uncommon gut microbiome compositions were more typical in those resistant to drug forms of epilepsy. People with drug-sensitive epilepsy and healthy people both showed comparable gut microbiota compositions. It is interesting to note that those who experienced four seizures in a year had lower bacteria levels from the genera Lactobacillus and Bifidobacterium (Peng et al. 2018). Contrarily, the study discovered that people with drug-resistant epilepsy had a greater diversity of gut bacteria than drug-sensitive plus healthy controls (Peng et al. 2018).

In contrast to the findings of Xie et al., who found that newborns with refractory epilepsy had lower gut microbial diversity (Huang et al. 2019a), Huang et al.'s study found that Microbial diversity was higher in children who also had cerebral disability and epilepsy. According to Huang et al., Enterococcus, Bifidobacterium, Prevotella, Clostridium IV, Streptococcus, Akkermansia, Veillonella, and Rothia were also shown to be more prevalent. Parasutterella, Roseburia, Faecalibacterium, Blautia, Ruminococcus, Bacteroides, and Anaerostipes were also noted to be less prevalent. Additionally, it's critical to recognize that cerebral palsy and epilepsy are two distinct neurological disorders, and there may be confounding factors affecting the patients' gut microbiota (Huang et al. 2019a).

Little is known about how KD treatment affects the gut flora of patients with epilepsy. After 1 week of KD, 64% of newborns with epilepsy had a 50% decrease in seizure frequency, according to Xie and his colleagues. After KD therapy, the abundance of Bacteroidetes and Actinobacteria increased, whereas the abundance of Proteobacteria was markedly reduced. No variations in Firmicutes, however, were found.

At the genus level, Streptococcus, Barnesiella, Erysipelatoclostridium, Cronobacter, Enterococcus, Ruminiclostridium, and Alistipes dropped to a lesser extent, whereas Bacteroides, Prevotella, and Bifidobacterium increased. Another trial 20 drug-resistant epileptic children were part of another trial, and 25% of the children showed improvement and reduced their seizures by 50% but by less than 90%, 15% of the kids reduced their seizures by 90%. After 6 months of KD, 10% of the children were seizure-free.

After the treatment, their fecal samples were examined; however, the alpha diversity showed no discernible difference. Actinobacteria and Firmicutes experienced a drop, while Bacteroidetes experienced a large uptick (Zhang et al. 2018). Lindefeldt et al. conducted a new study on 12 children with refractory epilepsy who received KD treatment for 3 months. The results showed that 83% of children had improved cognition and motor function, and 42% had seizures reduced by more than 50%. However, the alpha diversity of their gut microbiota compositions did not dramatically change. Instead, they revealed a rise in the number of Proteobacteria (Bifidobacterium) and a decrease in the frequency of Actinobacteria (E. coli) (Lindefeldt et al. 2019).

Studies using animal models have also been done to look into the mechanisms underlying how KD controls the gut microbiota. In a mouse study, KD significantly altered the gut microbiome, largely by lowering alpha diversity and increasing the number of the species Parabacteroides and Akkermansia muciniphila.

The metabolite level was altered as a result of these adjustments to the gut flora, most notably a decrease in the blood and colon lumen levels of gamma-glutamyl amino acid and an increase in the brain's GABA to glutamate ratio, which protected against 6 Hz seizures and decreased spontaneous seizures in mice lacking Kcna1 that mimicked epilepsy. In order to assess the significance of gut microbiota in influencing the seizure, by employing mice bred in a germ-free environment or by giving them antibiotics, scientists also lowered the gut microbiota. As a result, even after KD administration, the mice with diminished gut flora show lower seizure thresholds. However, the seizure threshold rose when mice fed on KD and given antibiotics Parabacteroides merdae with Akkermansia muciniphila (Olson et al. 2018). The results of this study generally imply that the gut microbiota and KD both contribute significantly to seizure prevention.

8.3.1.2 Obesity

One of the diet programs developed expressly to assist obese persons in losing weight is KD. Chronic metabolic illnesses like diabetes, hypertension, and an elevated risk of cardiovascular diseases are all closely correlated with obesity (Tanaka and Itoh 2019). In addition to other factors, such as the makeup of our gut flora, an energy imbalance is the cause of obesity (Bouchard 2008).

A larger abundance of the bacteria Lachnospiraceae sp. 8_157FAA, Alistipes shahii, Bacteroidales sp. ph 8, and Alistipes senegalensis, is found in people who are not obese (BMI < 30 kg m^{-2}). It was suggested that some of these bacteria may be involved in the metabolic processes of galactose degradation, L-histidine biosynthesis, and L-lysin biosynthesis, all of which were positively connected with obesity.

As an illustration, the research found that this histidine synthesis cycle was closely related to S. thermophiles and C. aerofaciens. Further research was conducted on the gut microbiome of people with a high Body Mass Index (BMI) of 35 kg m^2 and those with a low BMI of 28 kg m^2. According to the findings, Lactococcus lactis, Streptococcus thermophilus, Actinomyces odontolyticus,

Collisella aerofaciens, and Granulicatella unclassified are the six gut microbiota species that are most effective at predicting severe obesity.

Overall, the Firmicutes (Dorea formicigenerans, Ruminococcus torques, and Ruminococcus obeum) are more prevalent, while the Bacteroidetes (Alistipes senegalensis and Alistipes shahii) are less prevalent in the obesity group (Meijnikman et al. 2020). Additionally, Turnbaugh et al. found that obese people had a generally lower diversity of gut microbes. In the gut of obese people, Actinobacteria were found in larger concentrations, while Bacteroidetes were found in lower concentrations.

The study also suggested that, in addition to hereditary variables, the gut microbiota of family members may contribute to the familial tendency of excessive body weight (Turnbaugh et al. 2009). Schwiertz et al. (2010) found a reduced F/B ratio in obese people, in contrast to other studies that found a high F/B ratio in obese people (Crovesy et al. 2020). Various factors, including genetic makeup, environment, food, and general fitness, can impact the complex community that makes up the gut microbiome. These complicating factors made inconsistent results in research on the gut microbiome inevitable.

In various clinical trials, the therapeutic potential of KD for obesity has been examined. KD was just as effective at helping people lose weight as a low-fat diet combined with the lipase inhibitor orlistat, according to a randomized controlled study including overweight or obese patients (Yancy et al. 2010). To treat obesity, a high-fat, low-carb diet like the KD can work in a manner comparable to calorie restriction (low-fat diet + orlistat). The interaction of diabetes mellitus, hypertension, hyperlipidemia, and obesity may increase the risk of cardiovascular illnesses (Ginsberg and MacCallum 2009).

Compared to a low-fat diet plus orlistat, KD dramatically decreased hypertension in fat patients, demonstrating a more notable reduction. Regarding the lipid profiles, patients in both diet groups had higher levels of high-density lipoprotein and triglycerides. The KD group had lower hemoglobin A1c and glucose levels than the control group (Yancy et al. 2010). The benefits of KD over pharmacological intervention with low-fat dietary intervention include being significantly simpler and less expensive, making it a possible treatment option for metabolic syndrome and obesity.

KD can efficiently lower weight, waist circumference, and BMI by up to 14%, whether a symbiotic is included or not. Additionally, the gut microbiome was altered by this therapeutic food plan's increase in microbial diversity. With KD, the proportion of Firmicutes increased while the proportion of Proteobacteria decreased. Furthermore, Ruminococcaceae and Mogibacteraceae showed an increase in abundance, whereas Comamonadaceae, Enterobacteriaceae, and Sinobacteraceae showed a drop in abundance. Additionally, a higher percentage of weight loss is correlated with an increase in the Bacteroidetes/Firmicutes (B/F) ratio (Gutiérrez-Repiso et al. 2019). In addition, Basciani et al. found that throughout 45 days of very-low-calorie ketogenic diets (VLCKDs) comprising whey, animal proteins, or vegetables, Bacteroidetes rose in abundance, whereas Firmicutes declined in overall abundance.

When comparing the different types of proteins used in KD, vegetable proteins and whey performed better at reducing the number of Firmicutes than animal proteins. On KD, patients with obesity and insulin resistance lost a substantial amount of weight and improved metabolic indicators such as cholesterol, blood glucose, and blood pressure (Basciani et al. 2020). Bacteroidetes were far more prevalent than before, following the completion of KD with a reduction in Actinobacteria and Firmicutes, according to a study by Ang et al. on obese (non-diabetics) patients (Ang et al. 2020).

These findings support the finding that obese individuals had higher Firmicutes abundances and lower Bacteroidetes abundances and that Bacteroidetes abundance increased as Firmicutes abundance decreased. KD may alter the composition of the gut microbiome. These findings are in line with the conclusion that KD could alter the makeup of the gut microbiome by raising Bacteroidetes and decreasing Firmicutes to make the intestinal environment more balanced. Obese patients were found to have higher abundances of Firmicutes and lower abundances of Bacteroidetes (Ang et al. 2020; Koliada et al. 2017).

8.3.1.3 Autism Spectrum Disorder

Autism spectrum disorder (ASD) is a neurological disability that primarily affects boys as opposed to girls in children. It is identified by chronic social communication challenges as well as repetitive and restricted behaviors in youngsters (Johnson et al. 2020). Numerous research has tried to figure out how gut microbiota and autism spectrum disease are related. Meanwhile, other research suggested that nutrition has a significant role in clinical manifestations of autism spectrum disease by modifying the gut flora (Davies et al. 2021; Johnson et al. 2020).

Children with autism have a reduced abundance of Firmicutes and more Bacteroidetes in their gut microbiome, according to De Angelis et al. When looking at bacteria by genus, autistic children had larger concentrations of Sarcina, Clostridium, and, Caloramater, while Bifidobacterium was more lacking (De Angelis et al. 2013). Additionally, Kandeel et al. 2020 Demo outlined the connection between autism and intestinal Clostridium species. The research revealed children with (ASD) have more of these microorganisms colonizing their bodies. More specifically, Clostridium clostridioforme and Clostridium difficile, which have been reclassified as Clostridioides difficile (now known as Enterocloster clostridioformis), exclusively appeared in autistic people's guts. But only healthy control children have Clostridium tertium in their guts (Kandeel et al. 2020). Consequently, there may be a link between intestinal Clostridia colonization and the (ASD) is getting worse and developing. Despite conflicting results, autism-related gut microbial diversity is still a mystery. De Angelis et al. showed that autistic children's gut microbiomes were more diverse than healthy kids (De Angelis et al. 2013). On the other hand, Kang et al. discovered that autistic

children had a significantly reduced amount of Coprococcus, Prevotella, and unidentified Veillonellaceae, as well as a less diverse gut microbiome. Prevotella was the predominant genus of these bacteria, and it was different in autistic and neurotypical kids (De Angelis et al. 2013). In one of Ahmed and his colleagues' most recent investigations, it was discovered that the alpha diversity in autistic children and healthy control children was comparable. Additionally, compared to the control group, the Firmicutes/Bacteroidetes (F/B) ratio was dramatically reduced in young people with autism and their siblings who are not autistic. Nevertheless, there was no conclusive evidence on the relative number of Bacteroidetes and Firmicutes. Furthermore, Prevotella's importance was highlighted again when a study found that autistic children had considerably reduced Prevotella to Bacteroides ratios (Ahmed et al. 2020). These results raise the possibility that one of the causes of (ASD) was an overgrowth of certain gut bacteria.

In a clinical experiment including 30 children with (ASD) who received KD for 6 months, the effectiveness of KD as a treatment for autism was proven. According to the results, 53% of participants showed only moderate to little improvement on the Childhood Autism Rating Scale, whereas 7% saw significant improvement. Patients with milder forms of autism reportedly improved the most with KD (Evangeliou et al. 2003).

El-Rashidy et al. examined the effects of KD and a gluten-free, casein-free diet in 45 autistic children over the course of a 6-month case-control study. The effects of the two dietary regimens on speech, sociability, cognition, and behavior, as evidenced by advancements in the Childhood Autism Rating Scale Test for treatment evaluation. Notably, the KD group demonstrated better behavior and sociability scores compared to the casein-free, gluten-free group (El-Rashidy et al. 2017).

There is little information on how KD affects the gut flora of autistic people. Despite this, research using animal models has provided encouraging evidence that KD changes the formation of specific gut bacterial communities, which may indirectly affect symptoms of autism. According to a study done on mice, KD enhanced the F/B ratio in autistic spectrum disorder resembling BTBR mice (Newell et al. 2016).

Then, the KD assisted in bringing the initially raised Akkermansia muciniphila population in BTBR mice back to normal. This bacterium is believed to have a favorable correlation with autism spectrum disease (De Angelis et al. 2013). It is interesting that after receiving KD, the overall host bacterial abundance was reduced by 78% in the cecum and 28% in the feces of BTBR mice. This indicated that KD ingestion altered the composition of the gut microbiome, confirming the KD's potential to mitigate the prevalent low F/B ratio phenotype of autism spectrum disease (Newell et al. 2016). In a further experiment, KD-fed BTBR mice showed improved sociability and communication while exhibiting less self-directed repetitive behavior (Ruskin et al. 2013). However, more investigation is still required to determine how KD affects human gut microbiota composition and confers health benefits to autistic people.

8.3.1.4 Alzheimer's Disease

Alzheimer's disease (AD) is the most common type of dementia, a neurological condition that progresses over time. This deadly condition has an unclear cause, no known cure, and no reliable treatments or prophylactic measures (DeTure and Dickson 2019). Neurofibrillary tangles and Amyloid plaques of tau proteins have so far been the only pathological and clinical indicators of AD. The focus of research has been on determining how amyloid peptides contribute to the onset and prevention of this condition (Osborn and Saunders 2010).

The neuropathological indications of AD include the accumulation of senile amyloid plaques and neurofibrillary tangles in the brain. Plasma and cerebrospinal fluid (CSF) frequently contain -amyloid peptides, of which a larger proportion is identified as amyloid-40 (A 40) and a smaller proportion as amyloid-42 (A 42) (Graff-Radford et al. 2007; Rusek et al. 2019). In Alzheimer's patients, a 42 may clump together and deposit in the brain, forming senile amyloid plaques. Forty-two levels are consequently decreased in the CSF of Alzheimer's patients (Graff-Radford et al. 2007).

Researchers are investigating the relationship between the gut microbiome and AD in light of the growing significance of the two-way communication between the gut microbiome and the brain. The gut microbiome may contain microbiome biomarkers for the diagnosis of Alzheimer's and targets for disease prevention (Abraham et al. 2019; Lee et al. 2018). In 2017, researchers discovered a reduced richness based on alpha diversity in the gut microbiome of AD patients, according to Vogt et al. Additionally, compared to healthy control volunteers, dementia patients with AD had Firmicutes and Actinobacteria with lower abundances and Bacteroidetes and Proteobacteria with higher abundances (especially the species Bilophila).

A greater genus-level abundance of Gamella, Phascolarctobacterium, Blautia, Bilophila, Alistipes, and Bacteroides in Alzheimer's patients was related to greater disease, according to cerebrospinal fluid (CSF) biomarkers. A higher level of phosphorylated tau (p-tau) in the brain, for example, signals more tangle pathology; a lower amyloid-42/amyloid-40 ratio (A 42/A 40 ratio) indicates more amyloid burden in the brain; and a higher phosphorylated tau/amyloid-42 ratio (p-tau/A 42 ratio) indicates more AD pathology. Lower abundances of Bifidobacterium, Adlercrutzia, Clostridium, and Turicibacter in Alzheimer's patients were found to be associated with increased AD pathology. Chitinase-3-like Protein 1 (YKL-40), a biomarker of AD, was also found to be related to a higher abundance of Bacteroidetes and a lower abundance of Firmicutes (Turicibacter, SMB53) (Vogt et al. 2017). Additionally, Cattaneo et al. found that the guts of older people with amyloid-related cognitive impairment had higher levels of pro-inflammatory bacteria (Shigella–Escherichia) and lower levels of anti-inflammatory bacteria (Bacteroides fragilis and Eubacterium rectale) (Cattaneo et al. 2017).

The composition of the gut microbiota may play a role in the etiology of AD. Therefore, altering the nature of the gut microbiota may have an impact on the deposition of amyloid in the brain, perhaps resulting in this disease's intervention.

The majority of studies have demonstrated that KD or medium-chain triglyceride improves cognitive function in Alzheimer's (Neth et al. 2020; Ota et al. 2019). According to recent reports, the benefits of KD include raising A 42 levels in CSF, lowering tau protein, and improving cerebral perfusion (Neth et al. 2020).

In a clinical study, the effects of the modified Mediterranean-KD (MMKD) and the American Heart Association Diet (AHAD) on adults with early stages AD had their gut microbiota compared with healthy controls (Nagpal et al. 2019). The baseline microbiome diversity did not differ significantly between those at risk for AD with mild cognitive impairment and those without, according to the study's findings.

However, compared to their cognitively normal counterparts, Patients in the group with mild cognitive impairment had greater Tenericutes, Proteobacteria, and Firmicutes levels, whereas their Verrucomicrobia and Bacteroidetes levels were lower.

After 6 weeks of MMKD, they looked into the impact on the gut microbiota and found that neither the cognitively normal nor the mildly cognitively impaired groups had substantial changes in Firmicutes, Bacteroidetes, or Proteobacteria.

However, there were a number of alterations at the family and genus levels following MMKD. For instance, a mild cognitive impairment group clearly showed a large decrease in Bifidobacterium (phylum Actinobacteria), and this impact outweighed AHAD.

Organic fecal acids like lactate and short-chain fatty acids (SCFAs) were linked to alterations in CSF indicators of AD in addition to microbial makeup.

The peripheral and central neurological systems may benefit from the decreased lactate levels and elevated propionate and butyrate SCFAs caused by MMKD. Above importantly, a bioinformatics tool projected that the MMKD will be linked to AD is associated with fewer gene families (Nagpal et al. 2019).

The use of (KD) as a treatment for various diseases has become more popular, but there are no standard guidelines for its application. However, researchers have suggested best practices for implementing the KD in studies (Kraeuter et al. 2020). The gut microbiome has been shown to play a role in the development of diseases such as epilepsy and Alzheimer's, and manipulating the gut microbiota through a dietary intervention like the KD could potentially help attenuate or prevent these diseases in the future. Patients with epilepsy and Alzheimer's have been found to have a higher proportion of Proteobacteria in their intestines, which can contribute to inflammation and autoimmune diseases (Pilla 2020).

8.4 Conclusion

Growing research supports the idea that diet, stress susceptibility, mental health, and mental function all have a direct impact on one another throughout life. However, there is a knowledge gap about how these impacts occur, and the evidence is correlational. New groundbreaking research on the symbiotic links between

nutrition and brain function is desperately needed to guide public health policy on diet. The creation of novel nutritional innovations and providing recommendations based on evidence to assist people in promoting and keeping their brains fit all through their lives will be guided by advances in our understanding of the mechanisms by which nutrition influences brain function and memory. Our healthcare systems will be more sustainably run if we encourage eating behaviors that boost mental health and identify and validate vital specific dietary components. Bettering the long-term viability of our medical systems and reducing the financial costs associated with weak mental wellness and cognitive decline will require the promotion of dietary practices that improve mental health as well as identifying and validating specific critical nutrients. The individual's diet may significantly impact how well they are able to avoid and treat their depression. Vegetables, fruits, fiber, seafood, whole grains, and legumes should be included in a diet that both prevents and encourages depression. Processed foods and added sugar should be limited. Support and assistance in changing people's eating habits may be beneficial in public healthcare nursing proactive care and health-promoting activities to increase depression. According to the outcomes of the current systematic review, the following recommendations may be made to encourage and prevent depression: people should be given advice on healthy diets that include increasing consumption of olive oil, fish, legumes, fruits, nuts, and vegetables while drastically reducing or eliminating processed foods, soft drinks, sweets consumption. Micronutrients in the diet are crucial for preventing depression. To promote and encourage changes in diets for depressive disorders, public health practitioners may profitably employ MI as an approach and technique (low evidence value).

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Chapter 9
Chocolate: Food for Mood

Mohamed Terra

Abstract Chocolate, revered as the "food of the gods," has a storied history dating back to the Aztecs, who used it for various purposes, including enhancing strength and treating fatigue. Over time, it transitioned from a medicinal beverage to a beloved indulgence associated with pleasure. Despite extensive research into its effects on mood, cognition, and behavior, premature conclusions often overlooked its complex pharmacokinetic properties. While containing psychoactive compounds like b-phenylethylamine and anandamide, recent focus has shifted towards methylxanthines, notably caffeine and theobromine, abundant in chocolate. Notably, chocolate consumption triggers the release of endorphins and dopamine, eliciting feelings of pleasure and reward. Immediate mood-lifting effects are attributed to sensory qualities rather than psychoactive substances, warranting investigation into conditioned responses over time. Understanding the pharmacological properties of chocolate's psychoactive compounds, notably caffeine and theobromine, is crucial. Their differing pharmacokinetics and affinities for adenosine receptors underscore the need for comprehensive research into their individual and combined effects on mood and cognition. Despite associations between chocolate consumption and depression, the causal relationship requires elucidation. Chocolate cravings, linked to neuroticism and atypical depression, serve as potential indicators of emotional states and coping mechanisms. In conclusion, while chocolate's psychoactive compounds hold promise for understanding its effects on mood and behavior, further research is needed to unravel their intricate mechanisms and long-term implications. Careful consideration of study design, participant characteristics, and contextual factors is essential to delineate the true impact of chocolate on emotional well-being.

Keywords Chocolate · Psychoactive compounds · Mood effects · Caffeine · Theobromine · Depression

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9.1 Introduction

Carl Linnaeus named it Theobroma cacao in 1753, which translates to "food of the gods." Chocolate has been used for medicinal purposes since the time of the Aztecs. The Aztecs used chocolate to increase their strength before military and sexual conquests, among other uses (Wilson 2010).

The Badianus Codex, written in 1552, mentions the use of cacao flowers to treat fatigue. From the sixteenth century until the early twentieth century, various papers consistently suggested that chocolate stimulated the nervous system of apathetic, exhausted, or feeble patients (Dillinger et al. 2000). Chocolate was consumed as a medical beverage until the eighteenth century. It later became closely associated with milk. Van Houten improved the digestibility of chocolate by mixing the beans with potash. This powder was later called cocoa and marketed as a nutritious food prescribed by doctors. Subsequently, industrial campaigns highlighted the benefits of chocolate (Wilson 2010).

During the mid to late twentieth century, scientific research began to investigate the supposed benefits of chocolate. The effects of chocolate on mood, cognition, and behavior were attributed to the psychoactive components that it contains. Among these components, b-phenylethylamine, anandamide, and related derivatives were the most widely studied due to their interesting pharmacodynamic properties. However, many of the conclusions that were drawn were made hastily, without taking into consideration the pharmacokinetic properties of these substances. This led to confusion between the mere presence of psychoactive substances and their effective biological actions after chocolate ingestion.

Chocolate not only has a rich composition but also highly enjoyable characteristics such as flavor and texture, which are influenced by its sweet and fatty composition. These qualities evoke strong positive reactions in individuals who consume it. Many studies have explored these qualities to understand why people like chocolate and how it can lead to emotional eating. Theobromine is a type of methylxanthine that is specific to chocolate. In the past, it was thought to have little to no pharmacological activity and was therefore not as interesting as caffeine. However, recent research has started to refocus on both caffeine and theobromine as potential pharmacological agents that can help explain the psychoactive effects of chocolate. Additionally, researchers are exploring how these two compounds interact with each other and whether they have any additive or synergistic effects.

This chapter aims to summarize the research on chocolate's psychopharmacological properties and its effects on mood.

9.2 Hedonic Effects of Chocolate and Orosensory Properties

Chocolate satisfies two innate preferences: a desire for a sweet taste and a craving for a creamy texture, making it one of the most enjoyable foods out there (Drewnowski and Bellisle 2007). While every food has its unique orosensory qualities, chocolate's specific composition makes it probably the most delectable food in the world. However, its palatability has been found to affect regulatory mechanisms of appetite control and also stimulate neural systems that are associated with drug dependence.

Some researchers even view foods that are high in fats and sugars as similar to drugs of abuse (Drewnowski and Bellisle 2007). Consuming food, especially sweet food, has been found to trigger the release of natural opiates (Grigson 2002). However, it is the taste and not just the presence of sweetness that appears to be the key factor in causing changes in the opioid structures in the brain (Levine 2006). Opioid antagonists are known to block the hedonically associated component of overeating (Drewnowski and Bellisle 2007). Apart from endorphins, other chemicals such as dopamine are also crucial in generating feelings of pleasure (Epstein and Leddy 2006). There is a suggestion that endorphins increase dopaminergic activity in the mesolimbic pathways, leading to a change in the reward value of food (Parker et al. 2006).

It has been suggested that the pleasurable effects of eating chocolate have a significant impact on mood changes immediately after consumption. Studies have shown that the positive changes in mood after eating chocolate are more pronounced within a short period, specifically 5–30 min after ingestion. This supports the idea that early mechanisms, such as the sensation of taste, contribute more to mood changes than psychoactive substances found in chocolate, which may take longer to have an effect (Macht and Dettmer 2006). Some argue that the positive emotions associated with chocolate consumption may not necessarily be due to its taste but rather to the anticipation of its psychoactive substances. To determine whether the positive effects of chocolate consumption are due to the nutrients or the psychoactive substances it contains, we need to investigate whether regular consumption of chocolate leads to stronger conditioned responses.

9.3 Chocolate's Psychoactive Compounds

Chocolate contains a lot of psychoactive compounds, which leads to many interesting theories. Researchers used to focus on anandamide and 2-phenylethylamine, but now they are more interested in methylxanthines. We know that there are potentially psychoactive compounds in chocolate, but just because they are there doesn't mean they have an effect. Because there hasn't been much research on these compounds, there is a lot of speculation but not enough solid evidence. Researchers need to

study these compounds more thoroughly to see if they have any real biological effects when consumed in everyday life.

9.3.1 The Chemistry Behind Theobromine and Caffeine in Chocolate

Methylxanthines are a group of psychoactive substances that are widely consumed around the world (Serra Bonvehí and Ventura Coll 2000). While caffeine is found in various products like coffee, tea, and guarana, theobromine is consumed only through cocoa. Unlike other compounds found in chocolate that can potentially cause psychoactive effects, methylxanthines, particularly caffeine, have been thoroughly studied in terms of their pharmacodynamic and pharmacokinetic properties. Early research initially suggested that Theobromine had no significant effects on the central nervous system (CNS), leading to its disregard (Joint Food Safety and Standards Group 1997). However, new research on Theobromine is emerging, which may provide exciting new insights. Chocolate is the richest food source of Theobromine and is the main source of Theobromine in our diet. A standard 50 g serving of dark chocolate is known to contain a range of 17–36 mg of caffeine and 237–519 mg of Theobromine (Shively et al. 1985; Brice and Smith 2002).

Theobromine slowly reaches its peak plasma concentration about 3 h after oral intake. Notably, absorption from chocolate is faster compared to capsules, leading to higher peak concentrations after 2 h. In contrast, caffeine is rapidly absorbed (about 30 min), with conflicting evidence on its peak concentration time (Mumford et al. 1996); when ingested in chocolate, absorption of theobromine is delayed, peaking approximately 1.5–2 h later, and resulting in lower maximum plasma concentrations (Mumford et al. 1994). The levels of theobromine achieved are about four times higher than the maximum plasma levels for caffeine (Basheer et al. 2004). Moreover, theobromine clearance rate is approximately half that of caffeine, with a rate of 1.2 mL/min/kg for acute administration. However, theobromine unexpectedly presents a decrease in clearance rate with chronic administration, going from 1.2 to 0.75 mL/min/kg (Smit 2011). This decrease is not consistent among individuals, with considerable variability observed.

The median threshold dose of caffeine in capsules is 18 mg (Basheer et al. 2004). Compared to capsule ingestion, the peak plasma levels of caffeine in chocolate consumption are approximately 75% lower. Therefore, the threshold for psychoactive effects from caffeine in chocolate should be higher than 18 mg. A regular chocolate bar contains around 36 mg of caffeine (Mumford et al. 1994), which is enough to produce subjective effects. On the other hand, the median discriminative threshold dose for theobromine is approximately 560 mg. A 50 g chocolate bar contains around 237–519 mg of theobromine (slightly less in milk chocolate). It's important to note that individual sensitivity may vary, and more research is needed in this regard.

It has been found that the minimum dose of theobromine that can cause a noticeable effect varies significantly, and for some people, it can be as low as 100 mg (Basheer et al. 2004). While scientists have assessed the minimum effective dose separately for theobromine and caffeine, their shared mechanisms of action may lead to additive or even synergistic effects. Therefore, lower minimum effective doses may be required for each compound when used together. This highlights the importance of further research in this area.

In terms of pharmacodynamic properties, both caffeine and theobromine competitively counteract adenosine effects at A_1 and A_{2A} receptors (Fredholm et al. 1999). While high doses of caffeine can also activate phosphodiesterase, this is typically not observed with normal human caffeine consumption (Daly et al. 1983). Generally, caffeine exhibits significantly higher potency compared to theobromine, with a ratio of up to 10:1. However, their specific affinities for adenosine receptors A_1 and A_{2A} differ. Theobromine is at least ten times less active at the A_{2A} receptor but only two to three times less potent at the A_1 receptor compared to caffeine (Fredholm and Dunwiddie 1988). Despite theobromine being present in higher concentrations in chocolate, with an average ratio of 10:1 compared to caffeine (Smit 2011), slower absorption and reduced bioavailability lead to peak plasma concentrations that diminish this difference to a 4:1 ratio. Consequently, it is reasonable to infer that theobromine is at least as potent, if not more so, than caffeine at A_1 receptors.

Adenosine serves as a pivotal homeostatic regulator, facilitating the adjustment of energy consumption to substrate supply within the central nervous system (CNS). Its actions within the CNS are multifaceted, with a predominant inhibitory effect on neurotransmitter release. Evidence suggests that adenosine more strongly inhibits the release of excitatory neurotransmitters compared to inhibitory ones (Weinberg and Bealer 2004). Adenosine A_1 receptors are widely distributed throughout the brain, with particularly high levels observed in regions such as the hippocampus, cerebral and cerebellar cortex, and select thalamic nuclei. Moderate levels of adenosine A_{2A} receptors are found in dopamine-rich areas of the brain, where they are colocalized with dopamine D_2 receptors (Daly et al. 1983).

Methylxanthines, such as caffeine and theobromine, enhance the turnover rate of monoamines, including noradrenaline. This results in increased firing rates of noradrenergic neurons in the locus coeruleus and mesocortical cholinergic neurons. Strong evidence implicates adenosine A_1 receptors in interactions with dopamine D_1 receptors, affecting neurotransmitter systems such as glutamate and GABA (Daly et al. 1983).

Research indicates that caffeine consumption at doses of 75 and 150 mg has been associated with improved mood and reduced tenseness. However, there remains controversy surrounding whether these effects are merely attributable to withdrawal reversal. Psychomotor and cognitive performances, encompassing tasks such as mental arithmetic, learning, reaction times, hand steadiness, and tapping rate, have been extensively investigated. Overall, there is a positive trend in performance across these tasks (Lorist et al. 1994), suggesting that caffeine may enhance sensory input and motor output without affecting central processing functions (Smit et al.

2004). Importantly, long-term caffeine administration can lead to adaptive changes in the brain, resulting in beneficial effects such as reduced seizure susceptibility despite acute doses increasing susceptibility (Daly et al. 1983). Moreover, accumulating evidence suggests that caffeine usage may mitigate suicidal tendencies, potentially acting as an antidepressant (Daly et al. 1983).

It has been asserted that methylxanthines serve as the primary psychopharmacologically active compounds in chocolate. In a well-designed study, encapsulated cocoa powder, representative of a 50 g dark chocolate bar, was compared to a placebo to assess its impact on mood, subjective alertness, and performance in reaction time tasks. The use of cocoa powder in capsules enabled the isolation of the effects of active compounds in chocolate from its orosensory properties. Significant effects were observed, particularly in enhancing energetic arousal and improving performance in simple reaction time tasks, although no effects were noted in rapid visual information processing tasks. Notably, a subsequent study administering capsules containing equivalent amounts of caffeine and theobromine, as in the cocoa powder capsules, yielded similar effects, providing clear evidence of the psychoactive effects of dark chocolate and the contribution of methylxanthines (Porkka-Heiskanen 2011). However, it's important to note that not all psychopharmacological effects of chocolate can be attributed solely to methylxanthines. Performance in other domains was not tested, thus limiting the ability to discern any psychoactive effects of additional compounds in chocolate.

In summary, methylxanthines in chocolate in biologically significant quantities are efficiently absorbed into the bloodstream and reach the central nervous system (CNS) to function as nonselective antagonists of adenosine receptors. This action impacts multiple neurotransmitter systems, including the dopaminergic system, resulting in effects on mood, cognition, and behavior.

9.4 Chocolate: Emotions and Mood

It is frequently asserted that chocolate has the potential to act as a stimulant, euphoriant, tonic, and antidepressant. Nevertheless, the impact of chocolate on the emotional state is a matter of widespread debate, and the underlying mechanisms responsible for any observed changes remain unclear. Chocolate can affect mood in various ways, both positive and negative. While it can bring about positive emotional changes, guilt is often associated with consuming chocolate due to cultural associations of negative body image. Thus, chocolate can elicit negative emotional changes as well.

A comprehensive cross-sectional study carried out in the United States, notable for its large scale and rigorous design, revealed a positive association between higher depression ratings and increased chocolate consumption, a trend observed across genders. Importantly, this association remained significant even after accounting for potential confounding factors such as caffeine, fat, carbohydrates, and overall energy intake. These findings suggest a distinct role for chocolate in

influencing mood, independent of its nutritional components (Eysenck and Eysenck 1985). However, it is important to note that this study design cannot establish causality between chocolate consumption and depression.

Following Liebowitz's concept of "hysteroid dysphoria," Parker et al. (Klein and Liebowitz 2006) suggested that chocolate cravings among individuals with depression served as a useful indicator of atypical depression, successfully identifying two-thirds of individuals exhibiting three or more symptoms of atypical depression. It is noteworthy that chocolate craving was found to be associated with the personality trait of neuroticism, particularly in terms of heightened irritability and rejection sensitivity. Additionally, individuals who craved chocolate perceived it as having a calming effect on anxiety and irritability, leading to increased utilization of other self-soothing techniques (Macht and Mueller 2007; Parker and Crawford 2007). Neuroticism, characterized by a propensity for experiencing negative emotions, has been linked to increased reactivity of the limbic system. Therefore, the craving for chocolate in individuals with depression may be a mechanism to restore emotional equilibrium through homeostatic strategies.

Chocolate consumption has been observed as a coping mechanism for managing negative moods, as evidenced by a study where a negative mood-induced state was alleviated after consuming chocolate. However, this effect was only evident when consuming palatable chocolate, not unpalatable chocolate. Nonetheless, it's important to note that this study primarily examined the immediate effects of chocolate consumption, highlighting the significance of its hedonic effects (Christensen and Burrows 1990). In instances where chocolate is ingested as a response to dysphoric states as part of emotional eating strategies, it may offer temporary relief but potentially prolong rather than alleviate the dysphoric mood (Parker et al. 2006).

Several studies have indicated that resisting chocolate cravings can lead to a more positive mood (Mahler et al. 2007). However, it's essential to interpret the data cautiously, and chocolate should not be prematurely dismissed for its potential antidepressant activity. Further investigation into chocolate's effects on mood is warranted due to the existing confusion in this area. Many conclusions about chocolate's mood effects have been drawn from observational studies and research focusing on high-energy or highly palatable foods, yielding varied results likely influenced by a diverse population consuming chocolate for different purposes. Numerous potential confounding factors must be considered. It's crucial to differentiate between individuals who crave chocolate and those who do not and define the subject's mood concerning chocolate ingestion. Questions regarding the timing and duration of effects, whether they are acute or chronic, and differences between short-term and long-term administration need to be addressed. Long-term effects of chocolate consumption on mood remain largely unexplored in clinical trial settings, and it's important to recognize that the absence of short-term effects does not necessarily indicate the same for long-term outcomes, as seen with antidepressant drugs that require several weeks to exert significant mood effects.

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Chapter 10
Measuring Mood in Nutritional Research

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Abstract In nutrition research, mood is frequently measured, typically using rating scales. Positive mood encourages consumption, so it's crucial to evaluate mood accurately. There is mounting proof that mood is influenced by nutritional elements such as high and less essential nutrients, such as vegetables, fruits, supplements, and eating habits. The purpose of this review is to take into account a variety of conventional and cutting-edge instruments for evaluating mood in relation to diet. We examine questionnaires that have been psychometrically validated to evaluate both specific moods (such as depression) and a variety of emotions (such as melancholy, anxiety, anger, and energy). We examine questionnaires that assess positive mood (such as vitality, happiness, and calmness), and we recommend that investigators should broaden their toolbox to encompass a wider scope of healthy indicators, such as gladness, eudaimonia, and satisfactory living, which is a good mood linked to meaning, engagement and purpose. The cutting-edge technological and methodological aspects of real-time mood assessments were examined using experience sampling techniques, daily diaries, as well as ecological momentary evaluation, which are suitable for measuring moods as they happen on a daily or momentary basis, for instance, via smartphones' use. We conclude by urging the incorporation of more cutting-edge platforms, with a focus on a variety of ambulatory techniques and sampling tactics. Real-time evaluation will continue to provide a scientifically sound method of evaluating the relationship between mood and food as it manifests in day-to-day living, opening our eyes to new possibilities.

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10.1 Introduction

Foods affect our physical health, but current research indicates that they may also have an impact on our mental health, giving rise to the scientific discipline of nutritional psychiatry. Energy must be available continuously for the brain. The food we eat provides that energy. To be candid, what we eat has a direct effect on our brain's structure and physiology, which consequently affects how we feel (Selhub 2022). Consuming nutritious foods rich in antioxidants, minerals, and vitamins gives nourishment to the brain and guards against oxidative stress, which is created when the body consumes oxygen and can harm cells. For instance, diets high in refined sugars are bad for the brain. They exacerbate oxidative stress, inflammation, and the body's ability to control insulin. A high-refined-sugar diet has been associated with decreased brain functioning and even aggravation of the signs of mood disorders like depression, according to numerous research. It's noteworthy that the relationship between mood and diet was not fully accepted by the medical community for a long time (Selhub 2022). Serotonin is involved in the regulation of mood, regulation of sleep, food control, and inhibition of pain. Since the gastrointestinal tract produces around 95% of the body's serotonin and is lined with 100 million neurons, the digestive system's inner workings not only aid in meal digestion but also regulate emotions. Additionally, the billions of "good" bacteria that constitute the intestine's microbiome significantly impact the operation of these neurons and how neurotransmitters such as serotonin are produced (Selhub 2022). The study of dietary aspects of mental wellbeing, and specifically the impact of food on how one feels, is gaining traction. A variety of food factors, such as chocolate, sodas, traditional Western diets, snacks, decreased vegetable and fruit consumption (Jacka et al. 2010; Rahe et al. 2014) and specific micronutrient shortfalls (Colangelo et al. 2014) have been connected to worse mood.

But what precisely is the mood? And how can nutrition experts use validated questionnaires to quantify it in a psychologically complex manner? In this review, we define mood and examine various techniques used to gauge mood in nutritional studies. We discuss tools that are frequently utilized in nutritional research. We explore the advantages and disadvantages of these widely used measures from a psychological standpoint and provide other instruments to gauge feelings of wellbeing, such as the psychological wellbeing scales that are comparatively underutilized in nutritional studies. Then, utilizing ecological momentary assessment, experience sampling, and internet surveys, we present unique techniques for tracking mood in real time.

10.2 Defining Mood

"Mood" and "emotion" are separate concepts in affect science. Strong affective reactions, known as emotions, are fundamentally communicative activities (Hammersley and Reid 2009) and typically have apparent behavioral implications, such as changes in facial expression (Greimel et al. 2006). Although this may not encompass all feelings, one approach to categorize emotions is based on their facial expressions: anger, sadness, happiness, surprise, disgust, and fear. According to Parkinson et al. (1996), moods are tender, sensational experiences that might not have an impact on behavior. Additionally, it's critical to distinguish between "transient mood," which changes over a short period of time, and "protracted mood," which lasts for several hours or days and is easier to gauge using a questionnaire (Ekkekakis 2013). Most studies containing the word "mood" in the title deal with persistent, typically depressive mood. To produce the phenomena of a moderately steady level from the underlying transient flood of feelings, reports and assessments of prolonged mood rely on and, in one way or another, average knowledge obtained from episodic memory. For instance, although depressed people also experience happy events and thoughts, they have unique memory as well as attention biases toward recalling sad occurrences and thoughts (Elliott et al. 2002). Since depression is a persistent mood, it is formed cognitively and entails selective attention to various types of experience, such as contemplation (Huffziger et al. 2013). In spite of the fact that depression is likely caused by a complex of cognitive, neurological, and metabolic factors (Graham et al. 2013; Preiss et al. 2013), it also has behavioral effects in addition to phenomenological ones. The short duration of transient mood makes it unpredictable by nature. A transient mood does not control awareness because if it does, it either grows powerful enough to show itself as an emotion in behavior or develops into a prolonged mood that permeates awareness and/or behavior over an extended period. The idea of a fleeting mood as a "state" may not be realistic (Hammersley and Reid 2009). Transient mood is, by definition, transitory and prone to change, whereas the word "state" denotes anything that rules awareness and has observable content. "Valence" is a term used in some affect studies.

10.3 Nutrition and Mood

Throughout the lifespan, nutrition has a significant impact on how the brain functions. According to Singh et al. (2014), adequate nutritional intake lowers the chances of Alzheimer's disease and cognitive decline as people age and promotes proper brain growth and neurodevelopment in early life. Over the past 50 years, there has been a significant advancement in our understanding of nutrition. Now, in developed nations, food is not only considered a basic need for survival but also a means of promoting mental health (Ordovas 2015). Numerous studies have been

conducted on the impacts of nutrition on cognitive performance/mental functions (such as memory, attention, reasoning, decision-making, and problem-solving) connected to information processing as well as knowledge application. Typically, these studies use measures of objective results, which include accuracy and reaction time.

Less research has been done on how nutrition affects subjective measurements of mental functions, like mood reported by oneself. The associations between mental health and diet have recently led to numerous investigations. Indeed, according to epidemiological research, following the dietary patterns of Mediterranean—frequent fruits, nuts, legumes and vegetable intake; limited intake of dairy products, eggs, and poultry; as well as only occasionally consuming meat (such as beef) that is red when raw—reduces the risk of developing depression. It is possible that eating breakfast following an overnight fast enhances cognitive performance and that enhanced cognitive function enhances rated mood. According to Emilien et al. (2017), eating breakfast generally improves mood compared to skipping it. This impact might be explained to some extent by the fact that coffee, a well-known psychostimulant, is frequently taken with breakfast in Western countries. The effects of caffeine on cognition, including reaction times, alertness, levels of attention, short-term memory, mental clarity, decision-making, and ability to concentrate, have been demonstrated in several studies (McLellan et al. 2016). Additionally, following the consumption of caffeine, an improvement in self-esteem and mood and a delay in the commencement of exhaustion have been noted (Rucci et al. 2011).

10.4 Mood and Carbohydrates

It is a well-known fact that eating a breakfast high in carbohydrates boosts serotonin production in the brain, which is thought to increase mood. A meta-analysis conducted not quite long ago (Mantantzis et al. 2019) found that carbs had no beneficial benefits on any element of mood. Effects on mood have been reported inconsistently in studies on simple carbs that lasted less than 24 h (Micha et al. 2011; Probst et al. 2012). The fact that some findings did not include blinded participants to what they consumed (Hammersley et al. 2007) may help explain why different studies produced different results. It is also challenging to evaluate alterations on a few mood items because many researches employ numerous mood measures and occasionally multiple questionnaires.

The fact that eating releases endorphins, reduces dehydration, and alleviates craving or a strong need for food and the cognitive impacts of abstinence from food are further challenges in this research (Ganio et al. 2011). Therefore, the evidence that a diet of a particular constituent alters mood compared to abstinence from food or fasting cannot be attributable to the meal's nutrient level.

10.5 Diet, Inflammation, and Depression

According to studies, persons with chronic inflammation can benefit from adhering to Mediterranean food patterns (Kastorini et al. 2011). The opposite is also true; high-calorie, saturated-fat meals seem to promote immunological activation (O'Keefe et al. 2008; Noble et al. 2017). Truly speaking, one way by which Western diets might have negative effects on the health status of the brain, including hippocampal dysfunction, cognitive deficit, and blood-brain barrier damage, has been proposed as the inflammatory effects of a diet rich in saturated fat and calories.

Since prolonged inflammation has been connected to a number of mental health issues, including mood problems (Yuan et al. 2019), this process also offers a route via which low-quality food can raise the chance of developing depression. Nevertheless, the causes of food inflammation and their effects on mental health remain a mystery. However, drugs that fight against inflammation, such as non-steroidal anti-inflammatory drugs as well as inhibitors of cytokines, have been proven in randomized controlled studies to considerably decrease the symptoms of depression (Köhler-Forsberg et al. 2019). According to Yahfoufi et al. (2018), certain dietary elements, such as polyunsaturated fats and polyphenols, as well as common dietary patterns, such as following the Mediterranean diet, might fight against inflammation. This increases the chance that some foods may alleviate or protect against the symptoms of depression linked to increased levels of inflammation (Borsini et al. 2017).

10.6 Brain, Gut Microbiome, and Mood

The impact of dietary habits on the gut microbiome—a wide term for the billions of microorganisms, including viruses, archaea, and bacteria—provides a more contemporary insight to how food might alter mental wellbeing. Utilizing hormonal, inflammatory, and neuronal signaling pathways, the microbiome communicates with the brain in two directions (Osadchiy et al. 2019). Due to the following observation, there is a hypothesis that changed interactions between the gut microbiome and the brain have an impact on mental health: A transfer of fecal gut microbiota from depressed man into rodents seems to induce animal behaviors that are hypothesized to indicate depressive-like states (Kelly et al. 2016). There is an alteration of emotion-like behavior in rodents as a result of altered gut microbiome (Cryan and Dinan 2012). Common depressive disorders in men are connected with changes in the gut microbiome. These researches imply that changed neuroactive microbial metabolites contribute to symptoms of depression. Diet is a potentially adjustable predictor of the functionality, variety, and relative abundance of the gut microbiome throughout life, besides antibiotic exposure and genetic variability.

10.7 Measuring Mood in Nutritional Research

In nutrition research, mood is frequently measured, typically using rating scales. Many meals are promoted and consumed with the premise that they alter mood, at the very least by being enjoyable and possibly also by having functional effects on the neurological system, even though the effects of food on mood are frequently brittle and difficult to repeat. Findings on nutrition are impacted by mood changes because these changes influence when and how people eat and drink, which can have a great impact on their health. Typically, mood is assessed using a questionnaire rating method. Levels of arousal or subjective energy, negative vs. positive mood or bad vs. good mood, and tension vs. tranquility are typical mood dimensions. To prevent fleeting moods from being affected by time and the procedures of filling out questionnaires, it would be suggested that the evaluation of transient moods must be in accordance with current mood theories, or other evaluations need to be brief and administrable rapidly. Simple and thorough assessments should be used; the method should be simple to use to reduce error and bias when it is repeated; and mood should only be evaluated in situations where theoretically non relevant cognitive factors that could affect the rating of mood have been taken into account and controlled. Over 30 years of nutritional study have seen the measurement of mood, but little progress has been made in establishing criteria for the selection and application of suitable assessment tools (Ekkekakis 2013). If we want to properly evaluate mood in the nutritional study, we need to respond to the following questions: If we want to assess how food affects mood, what should we measure? How should we measure it? When should we measure it? Should we assess a person's feelings while they consume a certain product or the impact that consumption has on how they perceive their surroundings, and should those assessments be made right away or later, thus including memory function? We know that odor perception and food preferences will be altered with time and repeated exposure (Köster and Mojet 2007; Delplanque et al. 2008); after all, what is recalled affects our later meal choice decisions.

10.8 Objective Mood Measurement

Contrary to self-reported/self-rating evaluation of cognitive performance (such as participants' self-rated perception of how quickly or accurately a task was carried out) and mood, which are frequently referred to as subjective measures, measures of cognitive and motor behavior (number of words remembered, reaction time,) and physiological parameters (variability of heart rate, concentration of salivary cortisol, and blood pressure). Focusing on psycho-physiological responses and facial expressions, the objective assessment of eating-associated mood has used relatively advanced technology, such as video cameras and the web, combined with specialized software that can analyze data. However, it is believed that using objective

measurements to identify mood is technologically challenging and only serves as a supplement to self-reports (Cardello and Jaeger 2021; Schouteten 2021). The major difficulties in objective mood detection are related to practicality, user comfort, data accuracy, and interpretation.

Typically, data collection occurs under artificial, controlled study circumstances that limit participants' freedom of movement and may be uncomfortable for them. For instance, face-reading experiments may demand that participants face the camera at a specified angle (such as 40°) and maintain eye contact with it at all times while drinking or chewing. In turn, psychological assessments sometimes call for fixing electrodes to the skin, such as on the finger, scalp, or palm (Horska et al. 2016; Pennanen et al. 2020). Due to this, the viability of the employed technologies is constrained, especially under more realistic study conditions, and the results might not be very applicable to actual situations of food intake (de Wijk and Noldus 2021; Cardello and Jaeger 2021). Even if variations in measured variables do really exist, study samples are still tiny and may not have the power to detect those (Mehta et al. 2021) because of the difficulties associated with feasibility.

10.9 Subjective Mood Measurement

Mood is usually thought to vary along bipolar and orthogonal valence dimensions (negative vs. positive) and activation/arousal. It can be defined as a widespread and prevailing affective state. Additionally, mood can be divided between persistent affective states (like a persistently low mood) and passing, cyclical ones (like a fleeting rise in vigor). Despite evidence that mood can be regularly assessed, mood is seen as an illogical assessment of the brain's output since it is essentially phenomenological. For instance, it has been demonstrated that some medicines (Mula and Sander 2007) and stimuli (Campbell and Ehlert 2012) consistently affect mood, as determined by questionnaires and scales' ratings.

Aside from the wellbeing questionnaires, which frequently entail prolonged, generalized affective mood conditions, many approved tools are on the ground to measure short-period mood states, and they are effective in capturing mood change due to different approaches of nutrition (Yoto et al. 2012; Pase et al. 2013).

10.10 Measuring Multiple Aspects of Mood

10.10.1 Profile of Mood States (POMS)

Different moods are targeted by different surveys in other cases. For instance, the POMS (McNair et al. 1971) is a 65-item rating scale that produces a total mood index as well as one positive index (Activity/Vitality) as well as five negative

indices (Agitation/Worry, Dejection/Depression, Hostility/Anger, Inertia/Tiredness, and Bewilderment/Confusion). On a five-point rating scale (0 = not at all, 4 = highly), respondents utilize a unipolar scale to score how much they have recently undergone or currently undergoing 65 affect states (such as sad, tense, furious, energetic, weary, and bewildered). Other POMS variants include the updated POMS 2, which includes Friendliness as the new scale (Heuchert and McNair 2004), the POMS 2-Y youth model for teenagers aged 13–17, as well as various condensed forms. The vigor subscale of the POMS, POMS 2, and their abbreviated versions, which includes the words "lively, active, energetic, cheerful, alert, full of pep," "vigorous," and "active," is a useful tool for measuring positive mood. If a nutritional approach was intended to enhance calmness, it would be limited because the subscale of vigor only evaluates activation of happy mood, which is higher and not lower. Nevertheless, mounting data point to a potential link between a healthy diet and high-activation happy mood conditions. Findings have shown that eating fruits as well as getting enough iron led to higher ratings on the POMS's vigor subscale (McClung et al. 2009; Carr et al. 2013).

10.10.2 Positive and Negative Activation Schedule (PANAS)

The Positive and Negative Activation Schedule (PANAS), formerly the Positive and Negative Affect Schedule, is another well-liked mood indicator. The 20-item PANAS scale is frequently utilized to evaluate and assess different negative affect (NA) and positive affect (PA) measures. The PANAS still comes in a ten-item, condensed model with five questions for NA and five for PA (Mackinnon et al. 1999). Despite the fact that this scale is very well-liked, researchers should exercise caution when utilizing it because none of the two aforementioned PANAS types measure emotions with smaller levels of activation, such as tranquility, happiness, or melancholy. The PANAS-X is an expanded version with 60 items that can be used to evaluate more specific emotions, such as more isolated lower-level activation states (such as melancholy, peacefulness, and exhaustion), but not all of them (Watson and Clark 1994). The 20-item PANAS has been utilized to investigate relationships between the status of folate, the status of zinc, and mood (McConville et al. 2005; Williams et al. 2008). Mediterranean meals (such as whole grains, vegetables, and fruits) have been linked to higher PA and lower NA in studies using the ten-item version of the PANAS (Ford et al. 2013).

10.10.3 Bond-Lader Visual Analogue Scale (VAS)

In nutritional intervention studies, mood is also measured using verbal and visual analogs. The 16-item Bond-Lader visual analogue scale (VAS) was recently used, as an example, to investigate the effects of multivitamin supplementation on

wellbeing and mood (Pipingas et al. 2013). VAS has 16 100 mm lines that are each joined by an adjective pair, such as happy-sad, at each end. According to their current subjective state, Participants evaluate the levels of agreement or disagreement with each descriptor, allowing for fine distinction around the scale (Bond and Lader 1974). The measurement of scores is the distance from the negative anchor. In studies on appetite management, analog scales have been used successfully (Parker et al. 2004); in studies on appetite evaluation following a single meal, they have demonstrated high reproducibility, power, and validity (Flint et al. 2000); and in studies on mood disorders, they have demonstrated good validity and reliability (Ahearn 1997).

10.11 Measuring Positive Mood and Psychological Wellbeing

In nutrition research, measurements of unhappy mood, melancholy, and anxiety are significantly more prevalent than those of contentment and satisfaction of life. However, mounting proof exists that diet-related factors might as well contribute to these feelings of wellbeing. In research involving more than 80,000 Britons, a significant relationship between eating fruit and vegetables and having a higher level of life satisfaction was discovered that could not be explained by health or demographic characteristics (Blanchflower et al. 2013). Contrary to popular belief, these bad and good mental states are not two sides of the same coin. Not just the absence of despair or anxiety but also an ideal degree of emotional experience and functioning is what is meant by wellbeing (Deci and Ryan 2008). It is illogical to ask if a healthy diet boosts happiness above and beyond any negative effects it may have on ill-being. We suggest a number of psychometrically verified wellbeing metrics. Some assessments focus on hedonic wellbeing, or if a person is content with their life and feels joyful (Veenhoven 2003). The Fordyce Happiness Measures' first question, "In general, how happy or unhappy do you usually feel?" (Fordyce 1988), asks respondents to rate their feelings on a scale from zero (highly sad) to ten (highly joyful), as well as the Subjective Happiness Scale-SHS which is four-item (Lyubomirsky and Lepper 1999).

The Psychological Wellbeing Scale is among the frequently utilized tools to assess eudaimonic wellbeing measures. It encompasses six elements of eudaimonic wellbeing, including self-acceptance, positive relationships with others, personal growth, and environmental mastery (Ryff and Keyes 1995). There are two formats that are appropriate for researching eudaimonic wellbeing: a shorter 18-item variant and a longer 42-item format. It entails statements such as "In general, I feel in charge of the situation in which I live" (mastering the environment) and "Some people wander aimlessly through life, but I am not one of them" (purposeful living). The Flourishing Scale is eight-item (Diener et al. 2010); it is another shorter option. It contains statements such as "I lead a purposeful and meaningful life" and "I am optimistic about my future" which entails key elements of a successful life. Responses of the participating persons are rated from one (highly disagree) to seven

(highly agree) scales. A higher score indicates greater flourishing; the overall score ranges from 8 to 56 (Conner et al. 2014). Another helpful measure for assessing psychological wellbeing is the Warwick-Edinburgh Scale, which consists of 14 items (Tennant et al. 2007). This scale exclusively considers positive psychological effects and incorporates both hedonic and eudaimonic viewpoints. According to the scale, the highest level of wellbeing was linked to consuming roughly seven servings of fruits and vegetables daily (Blanchflower et al. 2013). Psychological states' wellbeings are not just the opposite of negative psychological states. We advise including positive wellbeing indicators in nutrition research to facilitate new scientific findings.

10.12 Innovative Real-Time Mood Measurement

Utilizing "real-time" or "near real-time" mood assessments is one of the fascinating discoveries in nutritional research. In most studies, participants are told to report their mood in terms of general traits (i.e., how they typically feel), either on past notes, for instance, the previous day(s) or in a future at a specific period of the day, typically in relation to when they eat a meal or take a supplement. Using technologies like internet diaries and smartphones, real-time assessment of mood allows scientists to monitor mood every day or on moment-by-moment patterns for an extended duration (often 7–28 days). For the purpose of a nutrition study, this last point is crucial. In comparison to the reported mood during a 7-day recall timescale or more, dietary treatment or micronutrient intervention should have timely or effective impacts on reported mood in close to real-time (Pipingas et al. 2013). This is because, according to Rooney et al. (2013), underlying neurotransmitter mechanisms may be impacted by dietary or micronutrient alterations. These processes are regarded to be more directly related to immediate and actual mood reactions than to delayed mood reflections (Conner and Barrett 2012). The way mood is altered after the treatment, such as rapid, delayed or gradual changes etc., can also be discovered by tracking mood over time.

The term "Experience Sampling Methods" (ESM) or "Ecological Momentary Assessment" (EMA) is frequently used to describe the real-time techniques for evaluating behavior, cognition, affect, and physiology repeatedly throughout time in naturalistic or unrestricted situations (Shiffman et al. 2008). A variety of real-time techniques can be applied in nutritional investigations. Daily diaries, behavioral observations, experience sampling, physiological functions' ambulatory monitoring, self-monitoring systems, physical activity or/and movement, and hardware and the tools used to quantify these features are some of the approaches.

10.13 Daily Diary Techniques

Daily diary techniques entail finishing a survey, also known as a diary, after a predetermined period, usually one time daily just before bedtime. Participants respond to interrogation on their daily encounters, including what they ate, how they felt, and other details. This usually lasts for 7–21 days; nevertheless, after about 14–28 days of data collection, the quality of the data may start to deteriorate, potentially because of participant stress. Should a long duration be needed, investigators could use an assessment burst pattern by conducting a survey every month for a few days to a week.

Due to their small frequency sampling, simplicity in administration (surveys of the internet), as well as capacity for several items, daily diaries are a favorite among academics. They are ideally suitable for assessing foods and mood simultaneously in nutrition research to explore, for example, how mood states are altered in reaction to, or ahead of, daily eating patterns.

Methods based on daily diaries could be very helpful for intervention findings. For instance, an investigation by Pipingas et al. (2013) reported no impact of daily supplementation with a high-potency multivitamin on measures of mood such as the POMS that were given at baseline, 8, and 16 weeks later.

Individuals in the active compound group, however, observed less anxiety, fatigue, and stress after they used mobile phones to record their moods at home, indicating that real-time evaluations could have more sensitivity to alterations of mood than chronic evaluations due to their temporal proximity (Pipingas et al. 2013). But as Pipingas et al. (2013) point out, the trends might be explained by the fact that observations from mobile phones were submitted immediately after post-multivitamin supplement daily intake, as opposed to the 2- and 14-month testing settings where participants skipped their daily supplement.

Standard Cronbach's alphas cannot be used to calculate reliability estimates for daily diary measurements due to their "nested" data that goes against the requirements of independence. The nested form of the data should be taken into account when computing reliability (Nezlek 2012).

10.14 Experience Sampling Methods

In an experience sampling method (ESM), persons are semi-randomly signaled between six to ten times daily, typically for many days and weeks, in contrast to a daily diary technique completed once daily. Participants respond to questions regarding their current circumstances at each signal. This sampling method is appropriate for capturing fleeting experiences that are ongoing, varied, and most prone to memory biases (such as pain). Examples of these experiences include rapid changes in emotional states. Even though experience sampling typically only

includes a small number of objects, which restricts the scope of the questions, reliability can be created by adding up individual items over time.

Typically, researchers aim to select data points and inquiries with strong face validity. To measure valence, researchers may, for instance, ask participants to judge their current moods as pleasant or unpleasant (0 being very, 9 being extremely), or they could aim to target distinct activation as well as valence levels (unhappy, energetic, tense, relaxed). The majority of studies on ESM encourage persons with an arbitrary scheduled signal. Nowadays, this signal is typically delivered through text messages or an auditory alert from a smartphone app.

10.15 Event Sampling

Event-dependent sampling, which involves the collection of data started by an individual after a specific occasion, is another helpful method. In studies on cravings and nutrition, this sampling design is useful. For instance, Lowe and Fisher (1983) discovered that female students who were obese had greater susceptibility to be involved in emotional snacking compared to their "normal weight" colleagues when they assessed their feeding as well as their mood using a form known as Food and Mood Self-Monitoring (FMSM) prior to food intake. As another illustration, Sayegh et al. (1995) asked their participants to report their mood and hunger using a computerized telephone system. A double-blind study was conducted on 24 premenstrual syndrome (PMS) sufferers to evaluate the impacts of various drinks on the symptoms of the condition. Before, 30, 90, and 180 min after consuming the beverages, participants quantified their answers to questions about their mood and appetite using the number pad on their phone. Additionally, phone interviews were used to perform cognitive assessments. The results demonstrate a substantial reduction in self-reported confusion, rage, depression, and strong desire for carbohydrates 1–3 h post-first consumption of a uniquely produced carbohydrate-rich drink recognized to raise concentrations of serum tryptophan during the menstrual cycle's late luteal phase.

The event contingent sampling techniques have also been employed to refute accepted notions about nutrition. In a sample of obese adult females with the disorder of binge eating, Stein et al. (2007) employed small portable computers to look into the connection between binge eating and negative effects. Contrary to earlier studies, they discovered that the negative effect did not significantly decline after a binge. Additionally, it was discovered that breaking a "food rule" was not the main reason for this eating disorder, in contrast to the widely accepted restraint idea. This study emphasizes the significance of testing the health behavior and mood contingencies in actual environments.

10.16 Sensor Sampling-Novel Method

Sensor sampling's use to measure moods as well as other mental conditions across time in day-to-day living is one of the most recent real-time techniques. In uninterrupted sensor sampling, measurement of activeness and physiological functions are continually captured within a predetermined period of time via audio or speech recorders or from the commonly available smartphones' built-in sensors in recent times. Together with self-reports of experience, data from continuous monitoring, such as movement or heart rate, is frequently helpful (Rachuri et al. 2011). In a similar vein, adaptive sensor sampling describes changing the sampling rate of these sensors in order to save energy, streamline processing as well as lessen the need for local memory (Rachuri et al. 2011). The user's mood can be inferred from the already available data in smartphones by using the mood sensor system to analyze the conversation history and the application usage patterns. For instance, the mood sensor accurately predicted the average mood of the user in a day with an accuracy of 93% as well as their abrupt mood alterations with an accuracy of 74% (LiKamWa et al. 2011). A study on the smartphones of individuals could provide experts in nutrition with essential information about their subjects' routines, activities, and natural behaviors. This record is made possible by fusing a log of the user's texting and calling patterns with the information from built-in sensors. Additionally, these software programs are increasingly available for use and modification by outside researchers to meet their study objectives. This can involve incorporating methods for nutrition researchers to track food intake. For instance, the University of Leeds developed the free smartphone app Mymealmate, which uses progress reporting, goal-setting, and self-monitoring of weight, exercise, and diet to enhance the weight loss of users (Carter et al. 2013).

10.17 Remote Food Photography Method

The Remote Food Photography Method (RFPM), which allows users to take pictures of plate waste and food selection, also has to do with employing the functions of built-in smartphone for findings in nutrition. In comparison to pen-and-paper food records as well as 24-h food recollection, this strategy improves people's estimation of their energy and food intake by minimizing past recollection-based mistakes (Martin et al. 2009). According to typical ESM guidelines, participants receive individualized prompts to remind them to take pictures of their meals at specific times. Comparing energy intake in a certain immediate circumstance to doubly labeled water (DLW), the most widely utilized metabolic indicator of free-living energy expenditure. It is a possibility to conduct enormous investigations with fewer financial and logistical constraints while obtaining accurate physical activity, mood, and nutritional data should RFPM be used alongside sense systems like EmotionSense (Rachuri 2012), MoodSense system (LiKamWa et al. 2011), or StressSense (Lu

et al. 2012). These programs show how commercially available cell phones can be used to continuously monitor users' emotional states, interactions, and mobility by combining machine learning and passive sensor data collection (Lathia et al. 2013). These technologies can be used by researchers to speed up data collection by automatically recording and categorizing information that will help them better understand how nutrition, physiological feed backs, and social interactions affect mood, emotions, as well as behavior.

10.18 Biases in the Mood Rating System

There are several interrelated causes of biases in the utilization of rating systems to evaluate mood, regardless of the selected method. Some of the most significant and well-known biases are listed here: set-point biases, biases resulting from the scale's granularity, biases resulting from the scale's labeling, and biases resulting from the things that can be rated (Ekkekakis 2013).

10.19 Set-Point Biases

The thing you report first restricts what you can report afterward. Your rating can only be raised by one point, for instance, if you first evaluate your hunger at 6/7 and then become more ravenous. You would have more room for your rating to rise if you had started out at a 2/7. A system that is unipolar, like the POMS, may present significant difficulties.

10.20 Granularity of the Scale Biases

Participants frequently do not use the entire scale when it includes a large number of points (100-point scales are occasionally employed). Individuals' responses may be categorized if the scale includes a few points. The suggested solutions are to use a blank line with well-labeled endpoints and to tell the individuals to mark a line based on their mood rating (for instance, using a visual analog mood scale). This results in the production of data that are best rated; however, it may cause participants who are less knowledgeable, less educated, and less conversant with the principles of graphical representation to give inaccurate and difficult-to-understand answers. Therefore, one should employ a seven or five-point scale with numbered points and well-marked endpoints. This results in ratings that are adequate and with fewer missing data.

10.21 Labelling of the Scale Biases

It is crucial that the endpoints of bipolar scales have distinct labels and are compelling opposites. The lack of distinctive, compelling alternatives for all conceivable mood adjectives makes mood assessments problematic. Is calm or sleepy the reverse of excited, for instance?

10.22 Items Available for Rating Biases

The worst mood could be caused by a variety of circumstances, including boredom, despair, low arousal, hypoglycemia, or dyspepsia. On the other hand, it is feasible to score mood using one rating from best to worst; however, this compels individuals to report any alteration in the subjective condition on this scale. On the other hand, mood can be assessed using up to 72 questions, which may demand judgments that are too finely tuned. For example, is it possible to be both "alert" and "drowsy" at the same time? A mood questionnaire should, in theory, address all pertinent facets of subjective state. This comprises evaluating the primary aspects of transient mood as well as typical aspects of subjective physical state, such as intoxication, illness, hunger, and thirst.

10.23 Recommendation

It is obvious that proper experimental set-up and appropriate choice of measure types are of the utmost importance; hence, nutrition experts must strive to use innovative real-time mood techniques and technological advancements. In a situation where there are many essential data points to be evaluated in between durations of assessment, it will become less acceptable in the near future to rely simply on pre- and post-test assessments of mood. Nutrition scientists should employ online or application-based daily diaries more regularly to document a variety of day-to-day measurements of mood as well as diet. Obviously, technology is incapable of taking the place of thoughtfully designed current measures, indicating the value of a multimethod approach. Given the nearly universal access to the Internet and cell phones, we also advise researchers to stay away from print diaries and paper booklets.

10.24 Conclusion

In nutrition research, mood can be measured in numerous ways. Some of them utilize more conventional methods, such as a paper and pen questionnaire, to examine traits and state moods. However, more recent technology developments and multimodal study methodologies have made it possible for us to better understand the complex interactions between dietary variables and mood. Real-time methods could be very helpful for investigations on treatment and intervention, where they have the potential to detect timely alterations in mood than the old measures. Additionally, by providing a more precise resolution of temporal sequencing than is possible with pre- and post-test results, these methods could assist nutrition researchers in demonstrating small alterations in mood due to dietary consumption. However, the technique used to measure mood in nutrition research needs to be appropriate for the study's objectives and its target audience. Most significantly, understanding the variety of mood measurements that are available to researchers is essential to the progress and success in the intriguing novel field of nutrition-mood-based investigations.

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Chapter 11
The Connection Between What We Eat and Our Brains Throughout the Whole Life Journey

Anhar Taha

Abstract The burden of cognitive impairment and mental illnesses is increasing daily because of modern lifestyles. Many studies have been conducted to understand the pathology of cognitive impairment and mental illness. Based on a good understanding of that pathology, many studies were conducted to determine if nutrition can play a role in hastening the progression of cognitive impairment and mental illness. Some studies were conducted to determine whether some cognitive impairment conditions or mental illnesses can be prevented from the start, especially when it comes to certain diseases that represent a real burden on society, such as AD, dementia, and major depressive disorders.

Other studies have shown the possibility of attaining better cognitive abilities and improving individuals' cognition and mental health. This will be reflected in the productivity of each individual in society, regardless of their age.

Although observational studies that examine the role of nutrition in mental health and cognition are diverse and the correlation between diet and brain development is obviously significant; unfortunately, there are few high-yielding RCTS. Consequently, the causal relationship between nutrition and brain function has not yet been concluded. In this chapter, we will discuss the harmony between the food we have daily and our brains.

Keywords Cognition · Mental health · Diet quality · Individual nutrients

11.1 Introduction

There are a lot of circumstances that affect our mental health and cognitive abilities. One of these principal factors is our daily diet habits, and its importance comes from the fact that nutrition is a modifiable factor that we can modulate if we want to enjoy

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good mental and cognitive abilities. Several clinical studies conclude that there is a reciprocal relationship between the gut and the brain. This harmony between the digestive tract and our brain is because of the effects of GIT hormones on the ability of neurons to strengthen their connections (Gómez-Pinilla 2008). Also, gut flora affects brain functions through its derived metabolites (Sun et al. 2020).

The relationship between a healthy diet and proper brain functions in early childhood and young adults is clear nowadays (Brennan et al. 2014). Poor nutritional status is associated with substandard performance in schools among children (Clarice et al. 1991). Successful cognition development is particularly important for children because it affects their innovation abilities, school performance, and creativity (Pianta Sandra and Mccoy 1997; Feinstein 2003).

It is important to make sure that our brain takes on essential needs during gestation, infancy, and childhood because they are the most important stages in building up cognitive abilities, while in young adulthood, we should seek high scores of cognitive abilities to be productive and efficient in societies. We should also seek healthier aging to reduce cognitive decline in that stage of life (Sünram-Lea and Owen 2017).

In this chapter, we will discuss the effect of individual nutrients and diet patterns on mental health and cognition in different age groups.

11.2 Impact of Individual Nutrients on Cognition and Mental Health

11.2.1 Individual Nutrients and Cognition

11.2.1.1 Vitamin B12

Vitamin B12 is present mainly in animal products such as meat, eggs, and dairy products (Watanabe 2007). A good intake of vitB12 helps to reduce homocysteine levels, which helps to preserve the blood–brain barrier (Rathod et al. 2016). Low plasma homocysteine levels hinder the ERK-MAP phosphorylation process, reducing neuronal damage (Poddar and Paul 2009). Children born to mothers with higher levels of vitamin B12 in the third trimester enjoy better cognitive abilities than their peers born to mothers with lower levels of vitamin B12 at the same gestational age, especially in color trial tests that tested their ability to sustain attention and cognitive flexibility while switching between different response sets (Bhate et al. 2008). Results were also encountered in another clinical trial, where they found that maternal levels of vitamin B12 were positively associated with favorable mental and social development after 2 years of follow-up with their children. Surprisingly, the current level of vitB12 at 2 years of age was unrelated to their cognition (Bhate et al. 2012). These findings go in line with a case study showing that a girl born to a mother with severe vitamin B12 deficiency due to her solely dependent vegetarian diet was found to have demyelination in different areas of her brain and

consequently arrested brain development and persistent primitive reflexes like the Babinski sign after 1 year (Lovblad et al. 1997).

These findings support the importance of vitamin B12 during gestation for the baby to have better cognitive abilities in the future.

Poor academic performance in school was encountered among children with vitamin B12 deficiency (Duong et al. 2015). In contrast, girls who have vitamin B12 included in their breakfast tend to have good scores in their exams (Ahmadi et al. 2009).

A study was conducted on a group of adolescents who depended on a vegetarian diet until they were 16 years old. There was an apparent improvement in their cognitive performance compared to their peers who depended on a diet deficient in vitamin B12 during their childhood (Louwman et al. 2000). Another study tracked the changes in the brain volume of a group of the elderly, aged 60 years and not suffering from any symptoms of dementia, and found that individuals with higher levels of vitB12 at the start of this study encountered less brain tissue loss over 9 years of follow-up by MRI (Hooshmand et al. 2016).

Although there is a positive association between vitB12 and cognition, there is no evidence supporting the good influence of vitB12 supplementation on cognition (Balk et al. 2007). The same conclusion has been reached by another study that reviewed 13 clinical trials that studied the cause-and-effect relationship between vitB12 and cognition and found the results inconclusive (Rosenberg 2008), so more clinical trials are warranted to prove the effect of high homocysteine levels resulting from vitB12 deficiency on impaired cognition among human beings (McCaddon and Miller 2015), proving that causality between vitB12 and cognition is crucial to cover this gap in clinical research and to take effective steps to stop the progression of cognitive impairment in susceptible individuals. Just imagine how it would be a throwback if we made dementia a preventable disease.

Till now, there is growing evidence that supports a strong correlation between vitB12 and cognition, and based on that, public health institutions may have to push towards following a diet rich in vitB12, especially for high-risk individuals who have biomarkers that indicate deficient vitB12 and for people in the initial stages of dementia (Smith 2008).

11.2.1.2 Iron

The relationship between iron and our brain can be complex, especially since there are many forms of iron status, such as iron deficiency anemia, non-anemic iron deficiency, and non-ID anemia. Understanding the effect of different forms on cognition is warranted although it might be challenging due to a lack of literature in some areas.

Iron can be obtained mainly from animal and plant diets. There are two types of iron present in diets: heme iron, which is found mainly in meat and fish, and non-heme iron in beans, nuts, and some fruits (Moustarah and Daley 2023). Iron is known to play a role in the myelination process, and its deficiency might cause changes in the temporal lobe and damage to mitochondria (Jáuregui-Lobera 2014).

A positive correlation was encountered between the hemoglobin concentration of a group of children less than 1 year old and their intellectual capacity between 3 and 5 years of age (Palti et al. 1983). Also, there is a positive correlation between iron deficiency and cognitive dysfunction in children under 2 years old. Among a group of girls in the primary school, it was found that girls with poorer school performance have a common iron deficiency anemia (Aukett et al. 1986). The cognitive abilities of a group of 5-year-old children who were suffering from iron deficiency in their infancy were evaluated, and the correlation between their iron status in infancy and their cognition of childhood was obvious, regardless of the correction of their anemic state at infancy, and this result may refer to the possibility of long-lasting outcomes of iron deficiency on the future cognition of children (Lozoff et al. 1991).

The evaluation of cognition in a group of early adolescents revealed that those who suffered from longstanding and severe iron deficiency anemia in their infancy performed badly in cognitive tasks (Lozoff et al. 2000), and this goes in line with the possibility that the previous study referred to.

The results of observational studies attracted attention to the intimate relationship between iron and cognition in children and the drastic consequences in cognitive abilities that are thought to be related to iron depletion during infancy in some way or another. This pushed physicians and scientists towards the acknowledgment of the cause-and-effect relationship between iron and cognition through clinical trials, among children below 2 years of age, the results from clinical trials did not support the evidence that prove that iron deficiency may be the cause for their cognitive dysfunction, and the limitation to these findings might be related to short-term trials and lack of large clinical trials that might prove that evidence, but the results of clinical trials for children above 2 years were more consistent and support the evidence of the causality relationship between iron supplementation and meeting good cognitive abilities among those age group (Grantham-Mcgregor and Ani 2001). Based on the previous results, public health policies should be directed towards ensuring adequate iron supplementation, specifically for children of school age. Health institutions should also encourage extensive long-term RCTs to examine whether iron deficiency in childhood is related to long-lasting limited cognitive abilities or not, and trials that experience how to prevent iron deficiency in this age group and the effect of that on their future intellectual abilities are warranted.

Studies that examined the correlation between iron and cognition in young and old adults are not diverse like children, but these few studies support the correlation between iron and cognition in these age groups as well as in children.

Based on meta-analysis iron biofortification is a promising intervention towards improving iron deficiency (Finkelstein et al. 2019). Public health authorities should give attention to the promising role of iron biofortification in the long-term management of the consequences of iron deficiency, especially on cognition. More studies are warranted to build strong and consistent evidence regarding iron biofortifications, and consequently, health programs can play a role in preventing future cognitive decline because of poor iron status among high-risk populations.

Among a group of young adults with IDA, there was a positive correlation between iron status and their cognition (Khedr et al. 2008), they examined their performance in cognitive tasks and found impairment in their verbal, intellectual, and memory functions, this positive correlation was also encountered by a recent study, where they noticed that young adults with good iron stores performed better in tasks that measured their working memory and cognitive executive functions (Raz et al. 2022), additionally cognitive evaluation of a group of young females revealed that there is a positive association between iron deficiency anemia and their cognitive decline (Cook et al. 2017), a clinical trial was conducted on two groups of young women, who were iron deficient and the other group was in good iron status, using iron supplementation as an intervention for the group with iron insufficiency, placebo for part of them and placebo for those with good iron status as control group; the results showed that participants whose ferritin level was improved after intervention, performed better in cognitive tasks that measured their abilities of alertness, retention of previously encountered information, being focused on a task over a period of time, working memory and inhibitory control, while those with higher hemoglobin level after intervention, only performed better in tests that examined their working memory and their ability to switch between different tasks (Leonard et al. 2014). Another important study proved that iron-biofortified beans improved the cognitive abilities of a group of young females who were suffering from iron deficiency anemia (Murray-Kolb et al. 2017). These results are consistent with the Indian randomized clinical trial on a group of young adults, where they found that the intervention group who consumed iron-biofortified pearl millet performed better in cognitive tasks than the control group who consumed just pearl millet (Scott et al. 2018).

11.2.1.3 Water

Good hydration was found to have a good influence on the cognition of school-age children. It was found that children who drank a higher amount of water did better in cognition tests, especially those testing their abilities to interpret and make sense of visual stimuli than their peers (Edmonds and Burford 2009). It was also observed that the cognition of two groups of dehydrated and hydrated children was compared by being tested in the early morning and afternoon; the group that was less dehydrated did better in cognitive tests than the other group that was more dehydrated in the morning (Bar-David et al. 2005). Another experimental study showed that drinking water positively affects the working memory of children and improves their alertness (Fadda et al. 2012). Good hydration for children was found to promote their ability to focus on the task and prevent distraction; this correlation indicates better cognitive control for well-hydrated children (Khan et al. 2015).

These results show a significant cause-and-effect relationship between water and cognition in children. Good hydration affects cognition in different domains. With water rehydration, children were found to have better visuospatial abilities and better short-term memory. Children who are allowed to drink water when they need it

and go easily to toilettes suffer less from dehydration than children in other classes who are prevented from drinking water during class (Kaushik et al. 2007). Knowing the bad consequences of dehydration on cognitive abilities, schools' policies should be directed towards the importance of water drinking for children during their classes and how it is crucial to facilitate that.

An important study showed that the positive effect of water on cognition is related to its physiological impact on brains and not to how individuals think of water (Edmonds et al. 2013a). Also, good hydration for thirsty adults affects their cognitive speed dramatically (Edmonds et al. 2013b). Another study was conducted among a group of young adults to examine the effect of dehydration on their cognition, the experiment was associated with a decline in memory and attention of this group, and these impaired cognitive abilities were improved by rehydration (Benton et al. 2016). The previous findings are consistent with the results of a clinical trial, which found that dehydration was associated with poor performance in tests that examined their abilities to visually track and respond to moving objects accurately, with good attention during the task, and efficiently execute motor actions in response to stimulus (Gopinathan et al. 1988). When the body is more than 2% dehydrated, cognitive abilities are affected (Gopinathan et al. 1988; Sharma et al. 1986). In another study conducted on a group of adults, it was reported that dehydration affects the attention of participants and their abilities to focus (Shirreffs et al. 2004).

In a study that compared the hydration status of two groups of elderly people and the effect of that on their cognition, it was obvious that the less dehydrated group performed better in cognitive tasks (Suhr et al. 2004). Among a group of elderly people, it was found that the more they were dehydrated, the slower they performed cognitive tasks (Ainslie et al. 2002).

Children and the elderly are exposed to the adverse effects of dehydration more than other age groups (Gandy 2012; Gaspar 1999). So, public health should hold campaigns to spread awareness about the importance of water to cognition, and special attention should be directed to these two age groups, who are more likely to be dehydrated.

11.2.1.4 Choline

Choline is an important micronutrient that is found in many kinds of food, but the liver of chickens, soy flour, salmon, and eggs are the richest in choline. It is recommended by the food and nutrition board of the Institute of Medicine of the National Academy of Sciences that individuals should have 7.5 mg of choline per kg daily (Zeisel and Da Costa 2009).

Choline plays a role in the process of CNS development because it is a methyl donor (Zeisel 2009). From that fact, there is growing evidence for the importance of choline in brain development and attaining good cognitive functions in cases of adequate choline consumption.

A prospective cohort study concluded that maternal intake of choline in the second trimester is positively associated with better scores in the visual memory

attained by their children by the age of 7 (Boeke et al. 2013). These findings are consistent with another prospective cohort study that found good cognitive function between infants aging (about 1 and a half years) born to mothers with higher levels of plasma choline measured after the second trimester (Wu et al. 2012). Also, according to the results of a double-blind randomized control study conducted on two groups of mothers, one group consumed twice as much choline as the other group, and the cognitive functions of children belonging to mothers who consumed higher amounts of choline were better than those of the other group (Caudill et al. 2018). Although these findings contradict an American prospective cohort study where they found no association between maternal intake of choline and child cognition at 3 years (Villamor et al. 2012). Another American randomized control trial found no difference between infants born to mothers who had choline during their pregnancy and their peers born to mothers who didn't have choline during their pregnancy (Cheatham et al. 2012).

An experimental study conducted on mice found that higher maternal intake of choline is protective against AD in the offspring as choline acts as a methyl donor and reduces homocysteine levels in the brain (Velazquez et al. 2020).

Although many studies performed on rats found strong evidence that supports the role of choline in achieving better cognition among the offspring, there is no strong evidence from human studies that supports the causal-and-effect relationship between maternal intake of choline and the better cognitive abilities of their children. The results of the studies are inconsistent, and more extensive research is warranted to confirm if there is a causal relationship between maternal choline intake and the cognition of the offspring (Wallace 2018).

A cross-sectional study conducted on 210 children ages 5 and older found no significant association between plasma choline concentration and cognition (Strain et al. 2013).

A double-blinded RCT was conducted on a group of young adults to examine the effect of choline consumption on their cognition. They found no significant difference in memory between the group that consumed choline and the other group that consumed placebo (Lippelt et al. 2016). These findings also contradict the causal-and-effect relationship between choline and cognition in rodents (McCann et al. 2006). And this indicates that extensive research on human beings is mandatory to properly evaluate the role of choline in the cognition of human beings. Another double-blinded randomized control trial conducted on a group of young adult females noticed improvements in visuomotor abilities in the group that ingested choline (Naber et al. 2015).

An American cross-sectional study conducted on a group of people aged >60 concluded that the risk of low cognitive performance among individuals with higher choline intake is decreased by 50% compared to those with lower choline intake (Liu et al. 2021). This goes in line with the results of another cohort study conducted on 1391 individuals, which found that higher concurrent choline intake is associated with better cognitive abilities in these individuals, while good previous choline intake is inversely associated with shrinkage of the brain volume and the appearance of lesions in the white matter of the brain (Poly et al. 2011).

It is obvious that there is inconsistency in the results of studies that have experienced the effect of choline on the cognitive abilities of human beings. Although the findings of studies conducted on animals seemed to be conclusive and confirmatory of the good effect of choline on cognition, that's why more worldwide randomized control trials are warranted to prove the effect of choline on human beings' cognition across the lifespan.

11.2.1.5 DHA

DHA is one of the active metabolites resulting from the denaturation of two important essential FAs (omega 3 and omega 6). The most important nutrients rich in these EFAs are peanut, seafood, and fish oil (Singh 2005). An experimental study conducted on animals revealed that DHA plays an important role in the process of neuronal growth, especially in the hippocampal region (Calderon and Kim 2004).

An American longitudinal cross-sectional study conducted on a group of pregnant women found that infants born to mothers with higher consumption of sea food have better cognitive abilities than other infants born to mothers with lower sea food consumption (Hibbeln et al. 2007). This is supported by the results of another double-blinded randomized control trial in which they compared cognitive abilities of infants born to mothers who consumed nutrients rich in DHA and other infants born to mothers who consumed nutrients rich in arachnoid acid and they found better cognitive abilities of infants of the first group (Helland et al. 2003). Another double-blinded RCT examined the effect of maternal consumption of fish oil as a source of DHA on the cognition of their infants at 2½ years and found better neurodevelopmental milestones in the infants of that group of women than the placebo group (Dunstan et al. 2008). A novel approach was used in the RCT trial to assess if there is an association between maternal DHA deficiency and the neurodevelopment of their children, and they found that infants aging 2 months born to mothers with good supplementation of DHA are blessed with better visual acuity (Innis and Friesen 2008).

DHA stores were reported to be depleted during pregnancy, and there are no reported adverse effects regarding maternal supplementation with DHA during pregnancy although there is no meta-analysis that reports the importance of DHA on the cognitive development of infants (Larqué et al. 2012).

Although the results of studies that experienced the role of DHA are inconclusive (Parenti 2014), the probable adverse effects of DHA depletion on mothers or babies may encourage us to recommend having nutrients rich in DHA during gestation. Further extensive research is warranted to cover the gap in this area and to know which factors influence mothers' responses to DHA supplementation and, consequently, the responses of their offspring. The coverage of that gap will help physicians intervene properly (Gould et al. 2016).

A clinical trial examined the effect of DHA on the cognition of children suffering from severe malnutrition, and after 6 weeks of ingestion of polyunsaturated fatty acids, there was a notable improvement in the cognition of that group of children (Stephenson et al. 2022). Specifically, daily intake of more than 450 mg (about half

the weight of a small paper clip) of DHA and above 6% of omega 3 was found to have a significant impact on the cognition of children and young adults (van der Wurff et al. 2020). The findings of the studies that examined the role of DHA on the school performance of children are inconsistent, but more than half of them showed a favorable effect of DHA on the performance of children in schools (Kuratko et al. 2013).

The memory of young adults seemed to be positively influenced by DHA consumption, as shown in an RCT conducted on a group of young adults (Stonehouse et al. 2013). In contrast, another RCT conducted on a group of young adult females found that DHA supplementation had an adverse effect on short-term memory (Benton et al. 2013). A systematic review and meta-analysis revealed a good influence of DHA on the memory of adults (Yurko-Mauro et al. 2015).

DHA was found to hasten the progression of hippocampal shrinkage in older adults (Zhang et al. 2016) and improve the memory of the elderly, who complain of a mild degree of cognitive impairment (Yurko-Mauro et al. 2010). In contrast, another RCT conducted over 6 months on a group of elderly people revealed that there was no significant difference in cognition between the group that used DHA as an intervention and the placebo group (Macpherson et al. 2022). Consistently, another RCT was conducted to assess if DHA had a role in preventing cognitive decline and AD. The results indicated that DHA couldn't hasten cognitive decline in the intervention group (Quinn et al. 2010).

Overall, although there are some differences in results related to DHA and cognition, in the majority of studies, DHA consumption appeared to have a good influence on the cognition of individuals across their lifespans. According to FDA recommendations, it is recommended to supplement DHA for susceptible populations 4 g daily (Lewis and Bailes 2011).

11.2.1.6 Carbohydrates and Cognition

Carbohydrates are present in the body in two forms: simple glucose and complex glucose in the form of glycogen. Glucose is an important source of energy that neurons in the brain depend on to fulfill their metabolic activity requirements (Levin 2009). It is also important for acetylcholine synthesis, which is an important neurotransmitter in the brain (Messier 2004).

In an English double-blinded RCT, children who ingested fluids containing glucose performed better in tasks that required memory than their peers in the placebo group although in this trial glucose seemed to have no significant difference between both groups regarding their ability to keep focused attention (Benton and Stevens 2008).

An interventional trial experienced the effect of different concentrations of oral glucose on memory. They used placebo (0 g of glucose), 15, 25, and 60 g, and the dose that appeared to have the most significant influence on young adults' memory was 25 g of glucose (Sünram-Lea et al. 2011). Another RCT was conducted to examine which part of long-term memory is affected by glucose ingestion. The group supplemented with 25 g of glucose showed better memory recognition than the placebo group (Sünram-Lea et al. 2008).

Going in line with most studies that point to the favorable influence of oral glucose ingestion on long-term memory, the episodic memory of a group of adolescents who ingested oral glucose was better than the placebo group (Smith and Foster 2008).

In many studies, the effect of glucose on cognition was noticed in young adults when the tasks were more difficult, but in the elderly, the change in cognition following glucose ingestion was easily observed (Messier 2004).

A double-blind RCT was conducted to compare the effect of oral glucose supplementation on two categories of elderly people: a group with mild cognitive impairment and a group with healthy aging. Interestingly, they found no difference between both groups regarding cognition; both groups showed improvement in spatial memory. Although mild cognitive impairment was encountered in those who had a higher fasting blood glucose level (Riby et al. 2009).

11.2.2 Individual Nutrients and Mental Health

Omega-3 fatty acids were found to be an effective treatment for children with major depressive disorder (Nemets et al. 2006).

A double-blinded RCT was conducted on a group of pregnant females suffering from major perinatal depression and concluded that there is no significant difference related to their conditions between the placebo group and the other group that tried fish oil as a source for omega 3 (Rees et al. 2008). This is consistent with the results of another American study that found no difference in outcomes related to major depressive disorder in pregnant women between the two groups of placebo and omega 3 (Freeman et al. 2008). In contrast, other double-blinded RCTs conducted on adults with depressive symptoms found much greater improvement in symptoms in the group treated with omega 3 than in the placebo group (Su et al. 2008; Lespérance et al. 2011).

An important meta-analysis confirmed the role of brain lipids in the pathogenesis of depression, where polyunsaturated fatty acids were found to be depleted among depressed individuals (Lin et al. 2010).

A randomized control trial conducted on a group of young adults who were at very high risk to develop psychosis, they used omega 3 fatty acid as an intervention in one group and placebo in another group, the risk of developing psychosis in the placebo group was higher than the omega 3 group, indicating that omega 3 might have a protective role against developing psychosis specifically among higher risk population (Amminger et al. 2010).

11.3 The Impact of Diet Quality and Pattern on Cognition and Mental Health

Now, after reviewing the effects of each individual nutrient on our cognition and mental health, let's be more realistic regarding the topic of diet, cognition, and mental health. People do not depend on individual nutrients; no one goes to the

supermarket and buys individual nutrients; actually, they buy food. So, if we need to convey this message to the public, we need to talk about dietary patterns and qualities and the effect of those on cognition and mental health (Allès et al. 2012; Tangney and Scarmeas 2012).

It would be easier in practice for physicians to instruct people about what they should have and what they shouldn't have to enjoy good cognitive abilities and mental health across their lifespan.

11.3.1 Diet Quality and Cognition

In a study that experienced the overall role of diet quality on cognition, poorer outcomes regarding verbal learning and memory were associated with lower HEI 2010 scores. For people living in poverty with low HEI 2010 scores, it was found that poor diet quality has a negative influence on cognitive flexibility and attention (Wright et al. 2017). This means that good diet quality has a good impact on verbal learning and memory. In a Greek study conducted on children, there was a positive association between bad performance in school and poor ingestion of a healthy diet like the Mediterranean diet, which depends mainly on fruits and vegetables (Vassiloudis et al. 2014).

Among a group of children aging from 6 to 8 years, there was a strong correlation between an unhealthy diet and improper cognition (Haapala et al. 2015). Whereas ingestion of a fatty diet, specifically one rich in polyunsaturated fatty acids, is associated with the good cognitive abilities of young children (Zhang et al. 2005).

Western diets are associated with hippocampal dysfunction; which affects mainly cognitive functions related to memory (Kanoski and Davidson 2011). Whereas ingestion of polyunsaturated fatty acids such as omega 3 is associated with proper hippocampal functions, specifically those related to tasks that require memory (Baym et al. 2014).

A prospective study conducted on young adults revealed that a western diet that depends on unhealthy refined foods is associated with poorer cognition (Nyaradi et al. 2014). A Spanish cross-sectional study emphasizes the strong correlation between western diets and better educational attainment (Esteban-Cornejo et al. 2016).

Based on a systematic review, it is recommended to follow the Mediterranean diet as a preventive measure against bad academic performance and cognitive impairment (Petersson and Philippou 2016). Public health should be directed towards spreading awareness among the population to follow healthy diets such as the Mediterranean diet as protective measures against developing dementia and AD, which represent a huge burden in society.

11.3.2 Diet Quality and Mental Health

An Australian prospective cohort study conducted on a group of young adults over a period of 4 years found a positive correlation between healthier diets and mental health wellbeing (Jacka et al. 2011a).

Individuals who consume refined diets, which are rich in processed food, are more likely to suffer from depressive symptoms as they age, while the risk of catching depression is much lower among individuals who consume unrefined diets (Akbaraly et al. 2009). This is consistent with the results of another Australian study that emphasizes the strong association between poor diet quality and mental illness (Jacka et al. 2010). Healthy diets that depend mostly on fruits and vegetables are associated with a lower prevalence of depression (Nanri et al. 2010; Jacka et al. 2011b).

A longitudinal study conducted on a group of old adults revealed that an unhealthy diet is associated with hippocampal shrinkage while proceeding in age (Jacka et al. 2015). Hippocampal atrophy was notable among a group of depressed elderly (Steffens et al. 2000).

A systematic review of 12 cross-sectional studies confirms the strong and significant association between poor diet quality and mental illness among children and adolescents (Brennan et al. 2014) although the cause-and-effect relationship between a healthy diet and mental health has not yet been concluded due to a lack of RCTs and interventional studies.

Diets that are based on vegetables, fruits, and other foods are recommended by another systematic review and meta-analysis as preventive interventions against depression (Lai et al. 2014).

11.4 Conclusion

To conclude, the digestive tract and our brain are correlated to each other, so our daily diet definitely affects our mental health and cognition. Through good daily habits in our food, we can be blessed with better cognitive abilities, we can improve the individual performance in society by improving his mental health, and we can reduce the burden of some diseases such as depression and ADHD that might hinder individual progression. Taking care of diet quality is extremely essential for the childhood age group, and it is also essential for elderly people to attain healthier aging and reduce the burden of some diseases, such as dementia.

Awareness regarding the importance of a healthy diet is not only for the bodies of the offspring but also for their minds as well, and we all know the common proverb “Prevention is better than cure.”

11.5 Implications and Future Directions

Public health authorities should launch screening programs to assess the nutritional status of populations and screen for deficiency of essential nutrients such as vitamins and omega 3.

An awareness campaign should be held by professional physicians to illustrate the long-term consequences of following unhealthy diets across the lifespan.

Through reviewing the existent literature, we noticed that there is a paucity of randomized control trials, consequently a paucity of causal-and-effect relationships. On the other hand, positive correlations were encountered significantly in most studies, so RCTS are warranted to build up strong evidence that supports the presence of a causal relationship between diets and brain functions.

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Chapter 12
Diet and Psychosis

Yara Ghanem, Afnan A. Almarshedi, Marwa Adam Abdelrahman Adam, Mario Eid, Ruta Karaliuniene, Sharad Philip, and Samer El Hayek

Abstract The link between nutrition and psychosis has long been an area of interest for scientists and researchers. Recent studies identified that individuals with psychosis may have lower levels of certain nutrients than those without the condition. This led to the suggestion that dietary interventions may be a potential treatment option for those with psychosis. This chapter delivers a wide-ranging summary of the current research on nutrition and psychosis. It overviews the most critical studies in the field, including but not limited to vitamins, minerals, and particular types of diet and their link with psychosis, the function of the gut microbiome, and hunger. While some studies hinted towards a link between certain dietary habits and psychosis, others have not. Additionally, the exact mechanisms by which nutrition may impact the progress of psychosis and its treatment are still not entirely understood. Nonetheless, the potential for nutritional interventions as a complementary approach for those with psychosis is an exciting area of research that warrants further exploration.

Keywords Psychosis · Schizophrenia · Diet · Nutrients · Inflammation

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12.1 Introduction

Schizophrenia spectrum disorders encompass a spectrum of severe mental illnesses with a lifetime prevalence reaching 1% (Van Os et al. 2010). The etiology of schizophrenia is complex and encompasses a multitude of biological, genetic, environmental, and social factors (Jablensky 2010). The disorder presents with two sets of symptoms, positive and negative; positive symptoms characterized by delusions and hallucinations, while negative symptoms can present as blunted affect, avolition, and alogia. This is typically accompanied by gradual functional and social deficits (Correll and Schooler 2020). Classically, the first episode of the illness is preceded by a high-risk state wherein the person faces reduced or brief psychotic symptoms or by a prodromal phase of depression, social withdrawal, and decline in functioning. While recovery potential from the first episode is elevated, over three-quarters of affected people will relapse. Psychotic relapse is usually triggered by a variety of factors, most commonly medication non-adherence, substance use, and stress. It varies in duration, intensity, and frequency based on many factors. Overall, about half of individuals with schizophrenia spectrum disorders will experience episodic in opposition to continuous disability (Larson et al. 2010).

People with psychosis and other severe mental illnesses have a decreased life expectancy that can reach 20 years, which has been labeled as the "scandal of premature mortality" (Thornicroft 2011), highlighting the importance of early and effective treatment. Conventional treatment of schizophrenia comprises pharmacological, psychosocial, and medical interventions (Kuipers et al. 2014). A cornerstone of treatment is antipsychotic medications, which mainly target positive symptoms but fail to enhance negative or cognitive symptoms of schizophrenia (Patel et al. 2014). As such, new strategies to prevent and treat all the spectrum of symptoms of psychosis have been of substantial interest. Nutrition and nutritional interventions in mental health have particularly received consideration over the past decade. The recent interest in nutritional psychiatry and the increased importance of providing adequate physical health care to individuals with psychosis has highlighted an essential role for nutritional interventions in schizophrenia spectrum disorder (Teasdale et al. 2020).

In this chapter, we take a closer look at the intertwining aspects between schizophrenia and nutrition. We interchangeably use the terms schizophrenia, psychosis, and schizophrenia spectrum disorder in our discussion. First, we examine the association between different types of vitamins and psychosis. We then look at dietary patterns in individuals with schizophrenia, including a discussion of refined carbohydrates and fibers, fats, proteins, amino acids, vegetables and fruits, n-acetylcysteine (NAC), phytonutrients, and minerals. In addition, we discuss various dietary choices such as the Mediterranean and ketogenic diets. We then discuss the interplay between schizophrenia, the immune system from one side, and the gut microbiome from another. We highlight gluten insensitivity and tolerance in psychosis before switching gears to the association between hunger, eating disorders, and psychosis. We then elaborate on the importance of a healthy diet in the physical care of

individuals with psychosis. Finally, we present the latest evidence on nutritional interventions tailored to the treatment of this disorder before concluding with a summary of clinical recommendations and insights for future research.

12.2 Vitamins in Schizophrenia Spectrum Disorders

12.2.1 Vitamin B Complex

Foods ranging from whole grains to animal products contain varying types of water-soluble vitamins known as vitamin B complex. They include vitamin B1 (thiamine), B2 (riboflavin), B3 (niacin), B5 (pantothenic acid), B6 (pyridoxine), B7 (biotin), B9 (folate), and B12 (cobalamin) (Suter 2020). These vitamins sustain different bodily responsibilities, specifically those that have a role in neuronal development and normal cell biology. For example, vitamins B2, B6, B9, and B12 are the primary sources of cofactors and coenzymes required for pathways related to the survival and proliferation of cells. These pathways result in the synthesis of myelin, DNA, RNA, and neurotransmitters (Selhub 2002). These vitamins also play a protective role in lowering neurotoxic homocysteine levels (Frankenburg 2007). Inadequate intake of foods that contain vitamin B complex represents one risk factor for developing psychiatric symptoms and disorders (Sarris et al. 2015). In particular, extensive research has shown that low levels of vitamin B6, B9, and B12 and high levels of homocysteine are associated with newly diagnosed and long-term schizophrenia (Zhang et al. 2016; Aucoin et al. 2020).

Deficiency in vitamins is a common cause of neurological symptoms, such as peripheral neuropathy and gait disorders, and psychiatric symptoms, including depression and psychosis (Wolffenbuttel et al. 2019). It was found deficient in patients hospitalized in psychiatry units without having hematological findings (Ssonko et al. 2014), with a prevalence of 5–30% (Lerner et al. 2006). Alternatively, psychiatric conditions can lead to vitamin B12 deficiency since the illness, particularly when severe, can cause poor nutritional status due to decreased appetite, diet, and metabolic requirements (Payinda and Hansen 2000).

Another vitamin B vital for neuronal functioning is vitamin B9 (Czeizel et al. 2013). Its deficiency elevates the risk of psychiatric and neurodevelopmental disorders (Mitchell et al. 2014), including schizophrenia (Cao et al. 2016). Similar to other vitamin deficiencies, folate deficiency in individuals with psychosis can be linked to having a diet insufficient in B9-rich foods, such as green beans, leafy vegetables, and nuts. One study, however, found that in patients experiencing first-episode psychosis, folate deficiency was not entirely explained by a deficiency in diet but also due to genetic differences in B9 bodily absorption (Kale et al. 2010; Hill et al. 2011). This was overcome by supplementing patients with an active type of folate known as L-methylfolate (Roffman et al. 2018).

Deficiency in vitamin B6, found in beef liver, fish, and other organ meats, is a known cause of neurological dysfunction (Clayton 2006; Miyashita et al. 2014). An essential form of vitamin B6 is pyridoxamine, which is known for decreasing carbonyl stress. A depletion of pyridoxamine will result in a decline in other forms of vitamin B6 and a resultant increase in carbonyl stress markers, a finding commonly observed in individuals with schizophrenia (Arai et al. 2010). Patients with psychosis who have a high level of carbonyl stress markers were found to display clinical features that resemble treatment-resistant schizophrenia, wherein they were more likely to be hospitalized, had a prolonged hospital stay, and needed a larger dose of prescribed antipsychotics. Alternatively, another form of vitamin B6, known as pyridoxal, is a coenzyme required to synthesize major neurotransmitters involved in the pathophysiology of schizophrenia, including dopamine and serotonin. This further hints at the association of vitamin B6 and its deficiency in the disorder (Miyashita et al. 2014).

Folate, cobalamin, and pyridoxine are essential for the activity of enzymes that decrease homocysteine levels in the body (Moustafa et al. 2014). Homocysteine is a neurotoxic amino acid that can lead to neuronal damage if it accumulates in cells (Reynolds 2006). It can also influence dopamine, serotonin, and acetylcholine levels and function (Moustafa et al. 2014). High homocysteine levels are an established risk factor for schizophrenia (Nishi et al. 2014), and this increase can be explained by a decrease in B6, B9, and B12 vitamins (Roffman et al. 2013), as well as genetic mutations in the gene affecting the metabolism of homocysteine (Frankenburg 2007).

Clinically, supplementation with vitamins B6, B9, and B12 in adjunct to antipsychotic treatment was found to be associated with improvements in total psychopathology in individuals with schizophrenia (Firth et al. 2017). A novel trial of patients with first-episode psychosis who were supplemented with a combination of these three vitamins compared to placebo re-iterated the above-noted results. Patients, notably those with elevated homocysteine levels, had improvement in attention and vigilance domains but no changes in their overall psychopathology or neurocognition (Allott et al. 2019).

Lastly, vitamin B1, which is found in beef, cereals, and beans, is not directly associated with schizophrenia, nor does its deficiency cause psychotic symptoms. However, individuals with schizophrenia are more prone to exhibit thiamine deficiency since they have a poor diet and tend to misuse alcohol (Casanova 1996). Thiamine deficiency can manifest as Wernicke Encephalopathy (WE) with the infamous triad of altered mental status, ataxia, and ophthalmoplegia (Harper et al. 1986). WE may be missed or erroneously diagnosed due to the symptoms being overlooked when the individual has comorbid schizophrenia (Casanova 1996). Therefore, it is crucial to remain vigilant of WE and thiamine deficiency in individuals with schizophrenia who present with comorbid alcohol dependence.

12.2.2 Vitamin A

Retinol and retinyl esters are a group of fat-soluble retinoids or vitamin A (Blaner 2020). Bioactive forms of vitamin A include retinoic acid and isotretinoin. The former is essential for animals, ensuring their healthy growth (Olson and Mello 2010). In humans, it plays a crucial role throughout the lifespan, from cell differentiation to the formation of the lungs, eyes, and other organs. As the body grows, it ensures proper cell communication, immunity, and reproductivity. Although it plays several functions in the human body, its most important role is ensuring vision and maintaining the functioning of the cornea and conjunctival membranes (Ross et al. 2020). Within the central nervous system, retinoids play essential functions in the adult cortex and other brain structures, including the amygdala, hippocampus, hypothalamus, and striatum (Lane and Bailey 2005).

The role of the retinoid system in schizophrenia has been discussed in the literature for decades. In an extensive review, Goodman related chromosomal loci of genes that control the retinoid cascade, including transport, delivery, and action to some candidate genes in psychosis (mainly those related to the dopamine and glutamate hypotheses) (Goodman 1995). More recent research highlighted findings from proteomic and large-scale genomic studies that link dysregulation of the retinoid system and psychosis (Reay and Cairns 2020; Reay et al. 2020).

Rich sources of vitamin A include eggs, fish, liver, and dairy products. The recommended dietary allowance to meet nutrient requirements varies from 400 mcg in newborns and babies to 900 mcg in adults (Institute of Medicine Panel on Micronutrients 2001). Clinically, decreased maternal vitamin A levels during the second trimester, but not the third, were found to be associated with an elevated risk of schizophrenia spectrum disorder (Bao et al. 2012). An old case report described the start of psychotic symptoms due to hypervitaminosis A in the setting of pseudotumor cerebri (Restak 1972). The first report of psychotic manifestations following an excessive intake of vitamin A described North Pole explorers who ate seal liver and polar bear meat (O'Donnell 2004). Bremner discussed multiple case series of isotretinoin-associated neuropsychiatric side effects, including psychotic symptoms, which resolved upon stopping the medication (Bremner 2021).

12.2.3 Vitamin D

Vitamin D is crucial for fetal growth, and its deficiency can impact different organs, including the central nervous system (Mattei and Pietrobelli 2019). In adults, vitamin D plays roles beyond calcium balance and bone metabolism. It has essential functions in neuroprotection, neurotransmission, and neuroplasticity (Shivakumar et al. 2015; Berridge 2018). It also reduces inflammation and oxidative stress caused by free radicals (Shivakumar et al. 2015; Tuohimaa et al. 2009).

Decades ago, scientists hypothesized that decreased levels of maternal vitamin D increase the risk of schizophrenia in the newborn (Mcgrath 1999). This was later supported by epidemiological studies showing that neonates with vitamin D deficiency were at increased risk for developing schizophrenia later in their lives in comparison to offspring with normal levels (Mcgrath et al. 2010; Eyles et al. 2018). More recently, a systematic review found a positive association between prenatal vitamin D deficiency and schizophrenia in the offspring (Upadhyaya et al. 2023). In adults, those with acute psychosis were noted to have decreased vitamin D levels when compared to individuals with schizophrenia in remission and healthy controls (Yüksel et al. 2014). Along the same line, in their extensive meta-analysis, Cui et al. showed that patients with schizophrenia and those with first-episode psychosis have an increased likelihood of vitamin D deficiency compared to healthy controls (Cui et al. 2021). However, this category of patients also tends to have poorer physical health, unhealthy diets, and lower activity, all factors that decrease vitamin D levels. The authors, thus, urged caution in any causal interpretation of this association between vitamin D deficiency and psychosis (Cui et al. 2021).

Many studies looked at supplementing vitamin D in individuals with psychosis. The DFEND randomized clinical trial is one of the significant studies that assessed vitamin D intake in 149 adults with early psychosis. Results showed that, despite the elevated prevalence of vitamin D deficiency in the sample, 6-month supplementation did not improve symptoms of psychosis (Gaughran et al. 2021). A meta-analysis of randomized controlled trials looked at nutritional interventions in psychosis; vitamin D supplementation was not associated with improvement in symptoms of psychosis (Xu et al. 2022). Cui and colleagues also concluded that there is no convincing evidence that vitamin D supplementation can treat symptoms of psychosis, as most available trials show inconsistent results (Cui et al. 2021). Using vitamin D supplements during the prenatal or neonatal periods as a method to reduce the risk of schizophrenia is also not recommended (Albiñana et al. 2022).

Notably, literature to date does not have any publications on psychotic symptoms occurring in vitamin D toxicity or hypervitaminosis D, indicating that neither deficiency nor excess states are causative for psychotic symptoms.

12.2.4 Vitamins C and E

Vitamin C (ascorbic acid) is a water-soluble vitamin found in fruits, mainly oranges, grapefruits, and other citrus fruits. It protects the body from the oxidative damage caused by free radicals. Vitamin C also assists in collagen synthesis, immune system support, and the synthesis of different monoamine neurotransmitters such as serotonin and norepinephrine (Englard and Seifter 1986; Harrison and May 2009). Another vitamin known for its antioxidant properties is vitamin E. It is a fat-soluble vitamin abundant in nuts, seeds, and green leafy vegetables (Zingg 2007). Along with vitamin A, vitamins C and E are significant antioxidants known to help prevent and progress many diseases, ranging from cardiovascular to neurodevelopmental

disorders. Recently, they have been a focus of nutritional psychiatry in light of their potential application as adjunctive therapy to decrease symptoms of psychosis and the side effects of antipsychotics (Adan et al. 2019).

Patients with psychosis tend to have a poor diet that is low in vegetables and fruits and high in fat and refined carbohydrates (Dipasquale et al. 2013). Such diet usually reflects less energy and diminished vitamin C and E levels (Mccreadie et al. 1998), in addition to other vitamin and mineral deficiencies (Valipour et al. 2014). One meta-analysis noted that patients with first-episode psychosis have a decrease in levels of multiple vitamins, including vitamin C (Firth et al. 2018a). In another study, high baseline vitamin C levels were linked to improved negative symptoms upon receiving aripiprazole. The authors suggested a possible adjunctive effect of vitamin C on treatment response, particularly negative symptoms (Myken et al. 2022). When it comes to vitamin E, one study found that individuals with schizophrenia consumed less vitamin E than their healthy counterparts (Mccreadie et al. 1998). More recently, Caldiroli and colleagues found that lower vitamin E levels were predictive of lifetime psychotic symptoms in patients affected by major psychiatric illnesses (Caldiroli et al. 2022).

One hypothesis on the pathophysiology of schizophrenia relates to oxidative stress. It entails an increase in free radicals that leads to oxidative stress, which causes oxidative stress-induced neuronal injury (Horrobin 1998; Mahadik and Mukherjee 1996). Clinically, patients with schizophrenia were found to have increased levels of oxidative stress and neuroinflammation at the beginning of their symptoms and before the start of antipsychotic treatment (Miller et al. 2011; Van Berckel et al. 2008). Oxidative stress can explain the development of symptoms of schizophrenia, and it can also explain the side effects of antipsychotics. Antipsychotics, mainly first-generation ones such as Haloperidol, can also cause an increase in free radicals, further adding to oxidative stress (Jeding et al. 1995; Subramanyam et al. 1990). In a physiological state, antioxidant activity can counteract the effect of free radicals and prevent cell damage. When antioxidant mechanisms are overpowered by excess free radicals, symptoms of schizophrenia can prevail and worsen (Wu et al. 2013; Lu et al. 2020). From this perspective, the interest in using supplements with antioxidant properties, such as Vitamins C and E, in managing schizophrenia has heightened (Mahadik et al. 2006).

In this regard, one double-blind placebo-controlled study found a reduction in oxidative stress markers in those who received vitamin C and atypical antipsychotics compared to a control group (Dakhale et al. 2005). An open-label pilot research of 17 patients with schizophrenia maintained on Haloperidol found improvement in positive and negative symptoms, as well as side effects from haloperidol upon supplementation with omega-3 fatty acids and vitamins C and E (Sivrioglu et al. 2007).

The role of vitamin E in managing antipsychotic-related side effects has been studied. An old open-label study found that vitamin E supplementation with antipsychotics is associated with a trend for the prevention of the emergence of neuroleptic-induced parkinsonism severity (Dorfman-Etrog et al. 1999). A Cochrane meta-analysis identified that, as per results from small trials, vitamin E might protect against deterioration of tardive dyskinesia but does not prevent it

(Soares-Weiser et al. 2018). An updated meta-analysis showed that vitamin E was associated with decreased tardive dyskinesia symptoms compared to placebo, particularly when supplemented at a low dose for a short duration. However, there was substantial evidence of publication bias in the studies conducted (Artukoglu et al. 2020).

Alternatively, excessive consumption of vitamins C and E can be harmful (Guallar et al. 2013). The recommended dose of vitamin C is 75 and 90 mg/day in males and females, respectively, while the dose of vitamin E is 15 mg/day for both genders. An excess of these vitamins may result in a pro-oxidant state that will inhibit antioxidant mechanisms, paradoxically increasing free radical formation. One study found that patients given high doses of vitamins C (1 g/day) and E (364 mg/day) had a decrease in red blood cell polyunsaturated fatty acids and clinically showed worsening symptoms of psychosis (Bentsen et al. 2013). A more recent case report highlighted how excess vitamin C intake led to the development of a brief psychotic episode (Gökçay et al. 2022).

12.3 Dietary Patterns in Schizophrenia Spectrum Disorders

12.3.1 Carbohydrates

Interest in the potential implication of carbohydrates in the development of psychiatric disorders has been on the rise. Several studies noted an association between ingesting high-glycemic index food and the risk of anxiety and depression. High glycemic index food can trigger reactive hypoglycemia, which may manifest as neuropsychiatric symptoms (Aucoin and Bhardwaj 2016). The ketogenic diet, characterized by low carbohydrate intake and high fat consumption, has been suggested as a possible approach to reestablish normal synaptic communication and ameliorate mental health, including in individuals with schizophrenia (Bostock et al. 2017; Sarnyai et al. 2019).

In animal models of schizophrenia, one study evaluated the link between a high-sugar diet and the development of psychiatric symptoms in adolescent mice. The authors found that a high-sucrose diet in mice deficient in the glyoxalase-1 enzyme, an enzyme implicated in the detoxification of sucrose metabolites, induced psychotic-like behaviors. This included symptoms of hyperactivity, poor memory, sensory processing issues, and disturbed interneuron function. In addition, the mice exhibited cerebral vascular damage and reduced brain glucose uptake, which was mitigated by aspirin supplementation. The authors found similar brain vascular damage in randomly selected patients with schizophrenia and bipolar disorder, suggesting that psychiatric illnesses may be linked to brain angiopathy instigated by various environmental stressors, including metabolic disturbances (Hirai et al. 2021).

Further supporting these findings, Dipasquale et al. found that patients with schizophrenia spectrum disorder tended to have a diet high in caloric intake and

saturated fats while alternatively being low in fruits and fibers (Dipasquale et al. 2013). The findings of Aucoin et al. were less consistent. In their analysis of 13 observational studies, only four studies reported a higher intake of total dietary carbohydrates in individuals with schizophrenia, while two reported a lower intake of carbohydrates and seven found no significant association. Alternatively, all ten studies assessing refined sugar and sweetened drinks reported a significant association with psychosis (Aucoin et al. 2020).

Research on the implementation of a low carbohydrate diet as a treatment for psychosis, mainly through the use of a ketogenic diet, is discussed in detail in the section "**Ketogenic diet**."

12.3.2 Fats

Multiple studies looked at the intake of fats and their role in patients with schizophrenia. For instance, one study on individuals with first-episode psychosis identified that participants exhibited higher saturated fat consumption in comparison to healthy individuals (Borgan et al. 2019). Aucoin et al. summarized the results of 17 observational studies that examined the dietary intake of total and saturated fats in individuals with psychosis compared to healthy individuals. Although findings were mixed, a more significant number of studies suggested that those with schizophrenia have a propensity for higher consumption of total or saturated fat (Aucoin et al. 2020). A more distinct pattern was identified when looking at essential fatty acids (EFAs), with five studies indicating a lower omega-3 fatty acid consumption and two studies suggesting a higher omega-6 fatty acid intake among individuals with psychosis (Aucoin et al. 2020). This trend has not always been maintained. One study comparing the consumption of omega-3 and omega-6 fatty acids in 146 community-dwelling participants with schizophrenia to healthy individuals found no significant difference (Strassnig et al. 2005). Alternatively, a prospective cohort involving 33,623 participants found that limited intake of both omega-3 and omega-6 fatty acids was linked to symptoms of psychosis in women (Hedelin et al. 2010).

Substantial research looked at the levels of EFAs in various tissue samples (blood, post-mortem brain tissues) in individuals with schizophrenia. These studies looked at the levels of several subtypes of omega-3 fatty acids, mainly docosapentaenoic, eicosapentaenoic, and docosahexaenoic acids (DPA, EPA, and DHA, respectively), as well as subtypes of omega-6 fatty acids including linoleic acid (LA), α-LA (ALA), γ-LA (GLA), and arachidonic acid (AA). Two meta-analyses specifically focused on the levels of EFA in the red blood cell membranes of individuals with schizophrenia compared to healthy subjects (Hoen et al. 2013; Van Der Kemp et al. 2012). A trend for lower levels was noted. In particular, compared to controls, medication-naïve patients exhibited reduced levels of DHA, DPA, and AA. Individuals maintained on typical antipsychotic medications had decreased levels of DHA, DPA, AA, LA, and GLA. Those receiving atypical antipsychotics

had lower levels of DHA. In addition, individuals taking any antipsychotic medication had reduced levels of DPA, DHA, and LA (Hoen et al. 2013, Van Der Kemp et al. 2012).

When it comes to fatty acid supplementation as a treatment of psychosis, preclinical studies provide evidence for the effectiveness of omega-3-enriched diets in decreasing psychotic behaviors in animal models of schizophrenia. For instance, one research found that oleanolic acid, found in olive oil, had the potential to improve psychotic symptoms in mice (Park et al. 2014).

Clinically, evidence for the role of EFA intake, status, or reserve in improving the clinical condition of individuals with psychosis has been noted decades ago. Three old case reports demonstrated positive outcomes upon supplementing individuals with schizophrenia with EFAs (Vaddadi 1979).

Regarding clinical trials, Aucoin et al. provided a summary of 28 clinical trials (sample size ranging between 9 to 320 participants) looking at the effectiveness and safety of omega-3 fatty acids (with treatment duration spanning from 6 to 104 weeks). The outcomes of the trials were diverse, with 13, 14, and 1 yielding positive, equivocal, and negative results. In 11 out of the 28 trials, no adverse effects were observed. The reported adverse effects were primarily mild and gastrointestinal (i.e., nausea, diarrhea, and indigestion), which were mitigated upon taking the supplement alongside a meal (Aucoin et al. 2020).

Deas and colleagues performed a meta-analysis of trials investigating the role of omega-3 use in the prevention of the progression to psychosis in high-risk populations. Due to the limited research, their analysis was based on only two positive trials (Deas et al. 2016). Three meta-analyses were carried out to look at the role of supplementing various omega-3 fatty acid formulations across the spectrum of schizophrenia. The three studies concluded that supplementation had no significant impact on the symptoms of chronic schizophrenia. However, it might offer potential benefits in terms of prevention or early-stage management of the illness (Sommer et al. 2014; Chen et al. 2015; Fusar-Poli and Berger 2012). A more recent systematic review found mixed data for the use of omega-3 fatty acids in first-episode psychosis. Supplementation in this group might be helpful for those with negative symptoms and elevated levels of oxidative stress and inflammation (Firth et al. 2018b). Along the same lines, Hsu et al. found that supplementation is effective in young individuals in the prodromal phase and have a low baseline of EFAs, particularly DHA (Hsu et al. 2020). More clinical trials that consider the stage of the illness and the specific type of supplemented EFA, among other variables, are warranted.

12.3.3 Amino Acids

Amino acids, obtained through protein intake, are crucial in synthesizing neurotransmitters. D-amino acids, which act as N-methyl-D-aspartate (NMDA) receptor modulators, have been used as possible augmentation strategies in resistant cases of psychosis (De Bartolomeis et al. 2022). In their review, Saleem et al.

discuss how disturbances in the levels of amino acids can be linked to the pathogenesis of schizophrenia (Saleem et al. 2017). Clinical research relating amino acids to schizophrenia spectrum disorders encompasses three types of studies: those looking at dietary protein intake in psychosis, studies assessing levels of amino acids in affected individuals, and interventional trials on the use of amino acids as adjunctive interventions.

Aucoin et al. note contradictory findings on protein intake in individuals with psychosis, with findings of lower intake, higher intake, or no relation between psychotic symptoms and intake of proteins (Aucoin et al. 2020). In studies looking at levels of amino acids, results were also contradictory besides a few specific patterns. Tryptophan levels were more likely to be low in affected individuals, and six experimental studies supplementing with tryptophan noted benefits in at least one domain of symptoms, including positive, negative, and cognitive symptoms and quality of life. Along the same lines, four studies showed worsened symptoms due to the depletion of Tryptophan (Aucoin et al. 2020). Tryptophan is the precursor of serotonin and a variation of its intake can affect serotonin levels in the brain, leading to depressive symptoms in patients and susceptible healthy controls (Van Der Does 2001).

Lysine supplementation improved at least one domain of symptoms in five studies. Alternatively, methionine levels were found to be increased in psychosis, and supplementation was associated with worsening symptoms (Aucoin et al. 2020). Methionine is crucial in methylation and 1-carbon metabolism, a pathway that requires adequate levels of vitamins B6, B9, and B12 (Frankenburg 2007). A disruption in this pathway, such as secondary to a vitamin deficiency, may elevate levels of neurotoxic homocysteine and interfere with glutathione synthesis, ultimately impacting mental health (Regland et al. 2004).

For glycine and serine, one meta-analysis found benefits in supplementing with glycine in positive and depressive symptoms and serine in negative and cognitive symptoms (Tsai and Lin 2010). Another meta-analysis found improvement in positive and total symptoms and negative and total symptoms when supplementing with glycine and serine, respectively (Singh and Singh 2011). This role is potentially mediated through glycine and serine's modulation of glutamatergic NMDA receptors (Tsai and Lin 2010).

In their systematic review, Bartolomeis and colleagues addressed the effectiveness of D-amino acids (D-alanine, D-aspartate, and D-serine) and related molecules (D-cycloserine, glycine, and sarcosine) in individuals with schizophrenia. We recommend that the reader refer to the systematic review for a comprehensive review of the trials and the provided discussion. The authors noted that amino acids have been typically explored in patients with schizophrenia who have had a limited response to antipsychotics and were ultimately maintained on clozapine. Results have been promising but necessitate future research, particularly in light of the trials' limitations, including the low sample size and methodological variations (De Bartolomeis et al. 2022).

Physicians can encourage patients to have a balanced diet that includes appropriate amounts of protein. This will ensure the provision of essential amino acids,

particularly tryptophan, lysine, serine, and glycine, for which there is most evidence. However, there remains a limited opportunity to modify the levels of these amino acids selectively, as dietary sources of proteins usually include all of them.

12.3.4 Fruits and Vegetables

Fruits and vegetables may enhance mental health because of their abundance of vitamins, phytonutrients, minerals, and other nutrients. In their extensive review, Aucoin et al. looked at studies assessing the intake of fruits and vegetables in individuals with schizophrenia spectrum disorder. They reported on the results of 22 cross-sectional studies looking at eating habits of fruits and vegetables in patients with psychosis and healthy controls (average sample size 506). Results were highly consistent, with 20 studies showing an association between low consumption of fruits and vegetables and psychotic symptoms (Aucoin et al. 2020).

One trial that included 102 individuals with schizophrenia provided participants with 6 months of free fruits and vegetables as an addition to their original diet, with or without instructions and support. Based on participants' self-reporting, the study found a significant increase in fruit and vegetable consumption at the end of the intervention. However, levels of carotenoids and vitamins B9, C, and E did not change. Moreover, 1 year after the intervention stopped, intake decreased to pre-intervention levels (Mccreadie et al. 2005). One explanation for these findings is that patients reported diet changes inconsistent with their real intake. This raises questions about accuracy and diet compliance. Findings also go along an issue frequently noted in individuals with mental illness. A recent study of 9914 patients with severe psychiatric illness found that intake of fruits and vegetables is deficient in this population group. Males, those below age 65, being unemployed, having poorer general health, and perceiving health as unimportant were all factors associated with never consuming fruits and vegetables or having less than five adequate portions per day (Lorimer et al. 2023).

Clinically, patients are always encouraged to boost their consumption of fruits and vegetables. In addition to their potential benefit in psychosis, they can positively impact several medical conditions common in this group of individuals. A higher intake is linked to decreased cardiovascular risk (Dauchet et al. 2006), type 2 diabetes mellitus (Jannasch et al. 2017), and all-cause mortality (Schwingshackl et al. 2017). More studies into the impact of fruit and vegetable intake on mental health remain warranted.

12.3.5 The Mediterranean Diet

The Mediterranean diet consists of plant-based foods characterized by a high intake of legumes, vegetables, beans, fruits, unrefined cereals, nuts, olive oil, and seafood, moderate consumption of dairy, chicken, and red wine, and low intake of red meat. Seafood is the favored source of animal protein (Siervo et al. 2021). This diet is linked to reduced inflammatory markers (Chrysohoou et al. 2004) along with a decreased risk of several chronic illnesses, including cardiovascular diseases and type 2 diabetes mellitus (Mantzorou et al. 2021). Essential components in the Mediterranean diet, such as nuts and seafood, are important factors in exerting antioxidant activities and neuroprotective properties (Duplantier and Gardner 2021). In addition, due to its rick content in fibers, omega-3 fatty acids, vitamins, phytonutrients, and antioxidants, it was found to have a protective role against depression, anxiety, and psychological distress (Sadeghi et al. 2021). It is also recommended in individuals with mental disorders, along with exercise and tobacco cessation, to reduce medication-associated metabolic and cardiovascular risk (De Hert et al. 2011b).

One systematic review looked at the association between mental disorders and consuming the Mediterranean diet. Only one study mainly looked at the association between diet and schizophrenia but did not find a significant relationship (Madani et al. 2022). However, the implementation of a Mediterranean diet in individuals with schizophrenia spectrum disorder is thought to help decrease the immune-related complications of psychosis and the metabolic side effects of antipsychotics. This positive impact of the diet seems to be modulated mainly by its high fiber and short-chain fatty acids (SCFA) content (Joseph et al. 2017).

Sugawara and colleagues found that healthy diets abundant in vegetables and fish were associated with lower body mass index in individuals with psychosis (Sugawara et al. 2014). In a recent study comparing the provision of a Mediterranean diet between individuals with first-episode psychosis taking antipsychotics and healthy individuals, although the former group was less likely to adhere to the diet, it acted as a prognostic factor for them having anomalous glucose levels (Vassilopoulou et al. 2022). Kowalski et al. particularly noted the difficulty of adhering to such a diet in deficit schizophrenia subtype, compared to non-deficit subtype and healthy controls, leading to a greater risk of developing obesity and metabolic side effects (Kowalski et al. 2022). Along the same lines, another study found that 60% of those with first-episode psychosis had limited adherence to the Mediterranean diet, again significantly associated with higher weight and cholesterol levels (Saugo et al. 2020). Theories that potentially explain this lack of adherence include the impact of antipsychotics on the dopaminergic system (Mathews et al. 2012), leading to a preference for highly palatable food, as well as the negative symptoms of the illness (Kowalski et al. 2022; Mezquida et al. 2018). Such findings have important clinical implications and highlight the relevance of enhancing adherence to the Mediterranean diet to advance the mental and physical outcomes of individuals with schizophrenia.

12.3.6 The Ketogenic Diet

The ketogenic diet is a low-carbohydrate (30–50 g/day), medium-protein (up to 1 g/kg/day), and high-fat (approximately 80% of total calories per day) diet which triggers a metabolic state known as ketosis (Dowis and Banga 2021). Initially developed to treat epilepsy, it has shown promising effects in other neurological and psychiatric illnesses (Jensen et al. 2020; Lutas and Yellen 2013). The ketogenic diet displays several relevant mechanisms of action: metabolic changes, anti-inflammatory and anti-oxidative effects, neurotransmitter modulation, and neuroprotection (Dowis and Banga 2021; Masood et al. 2022), all of which possibly contribute to its hypothesized therapeutic potential in schizophrenia.

- Metabolic changes: The ketogenic diet triggers a shift from glucose to ketone bodies as the chief energy source. This change offers an alternative source of energy for the central nervous system, leading to changes in brain energy metabolism and mitochondrial function (Lutas and Yellen 2013; García-Rodríguez and Giménez-Cassina 2021). These changes can have a therapeutic impact on psychosis. One review discussed the compromised glucose metabolism and mitochondrial dysfunctions in schizophrenia, resulting in impaired synaptic communication. It highlights how a ketogenic diet can be therapeutic in that regard by providing an alternative "fuel" to the brain. The review then builds on preclinical findings in genetic mouse models and clinical case studies of ketogenic diet improving psychiatric symptoms in patients with schizophrenia to assert this hypothesis (Sarnyai et al. 2019).
- Anti-inflammatory and anti-oxidative effects: In preclinical studies, the ketogenic diet decreased inflammation markers by suppressing various pathways, such as the NLRP3 inflammasome. It also acts as an anti-oxidant, reducing oxidative stress markers and enhancing endogenous antioxidant systems (Jiang et al. 2022).
- Neurotransmitter modulation and neuroprotection: The ketogenic diet affects several neurotransmitter systems associated with schizophrenia, including the dopaminergic and glutamatergic systems (Dahlin et al. 2012). In one preclinical study using mice with acute NMDA glutamate receptor hypofunction model of psychosis, the application of a ketogenic diet reversed behavioral abnormalities in rats. It particularly normalized pathological behaviors and led to weight loss and decreased glucose levels (Kraeuter et al. 2015). The diet also exerts neuroprotective effects, mainly through its anti-inflammatory and anti-oxidative effects, as well as the upregulation of neurotrophic factors and improvement of mitochondrial function (Jiang et al. 2022).

Clinically, the first assessment of the therapeutic potential of the ketogenic diet in schizophrenia was in 1965. In this pilot study, ten hospitalized females with treatment-refractory schizophrenia were supplemented with a ketogenic diet. This resulted in significant amelioration in their mean symptom scores after 14 days (Pacheco et al. 1965). Decades later, one case report discussed how the ketogenic

diet substantially benefited a patient with schizophrenia (Kraft and Westman 2009). In their extensive review, Włodarczyk and colleagues then proposed how, in individuals with psychosis, a ketogenic diet might improve the therapeutic response to antipsychotics (Włodarczyk et al. 2018). More recently, a retrospective study of 31 hospitalized individuals with severe mental illness showed that among the ten patients with schizoaffective disorder, implementing a ketogenic diet was linked to a significant improvement in scores on the Positive and Negative Syndrome Scale (PANSS) (Danan et al. 2022).

While keeping the above in mind, one should acknowledge the limitations associated with adhering to a ketogenic diet, which necessitates strict rationing of macronutrients and careful meal planning. This might be particularly challenging in the context of psychosis. In addition, care should be provided for any side effects, such as gastrointestinal disturbances and electrolyte imbalances, particularly in special populations, including pregnant females, those older than 65, and individuals with medical comorbidities (Firth et al. 2020).

12.3.7 N-Acetylcysteine

NAC is a derivative of cysteine, a sulfur-containing amino acid. It is an antioxidant precursor to glutathione and is known to reinstate glutathione levels in the body. The latter acts as the most ubiquitous antioxidant in the body. It neutralizes reactive oxygen species and maintains cellular oxidative balance (Dean et al. 2011). Adding to its antioxidant properties, NAC has shown potential for preventing dopamine and glutamate dysregulation. It has also been shown to modulate inflammatory mediators by acting as an anti-inflammatory (Dean et al. 2011).

NAC has been applied in the treatment of paracetamol toxicity for several decades and is now commonly used as a mucolytic and in the management of chronic obstructive pulmonary disease (Dodd et al. 2008). Based on the abovementioned mechanisms of action, NAC has been explored for potential benefits in psychiatry (Dean et al. 2011).

Many studies looked at the particular effect of NAC in psychosis. Yolland et al. discussed the literature reviewing cognitive impairment in schizophrenia, the association between cognition and oxidative stress, and the potential role of NAC in that regard (Yolland et al. 2020b). Clinically, Yolland and colleagues also published a meta-analysis of RCTs looking at the function of NAC in the treatment of schizophrenia. Their study included seven trials (220 individuals in each NAC and placebo group) and showed supporting evidence for using NAC (median dose of 2000 mg/day) as an adjunct to the standard antipsychotic treatment. The authors particularly noted that the effects of NAC were significant after supplementation for more than 24 weeks rather than for less than 8 weeks. Significant findings included the attenuation of negative symptoms (3 RCTs) and total psychopathology (2 RCTs) after 24 weeks of supplementation, along with improvement in working memory but not processing speed (3 RCTs). The authors suggested the need for long-term

maintenance with NAC for clinical benefit to be observed (Yolland et al. 2020a). Another meta-analysis found similar beneficial results of NAC supplementation on PANSS total score and negative and general subscale scores, in addition to significant improvement in attention and working memory scores (Kishi et al. 2023). An alternative meta-analysis of 594 individuals from eight trials found no evidence for NAC as an augmentation strategy in psychosis, regardless of whether supplementation was for more or less than 24-week duration (Zhang et al. 2023). One 52-week RCT of NAC (2000 mg/day) in individuals with schizophrenia refractory to clozapine ($n = 84$) found that NAC was not better than placebo on any clinical, cognitive, or quality of life outcome in this particular subgroup of patients with psychosis (Neill et al. 2022). The findings of Yolland et al. were later scrutinized in a review by Dr. Andrade, highlighting that results, although statistically significant, had limited clinical meaningfulness (Andrade 2022). In conclusion, it is premature to endorse the usage of NAC in routine clinical practice in the management of schizophrenia spectrum disorder. More robust long-term RCTs are necessary before making any endorsement for NAC in psychosis.

12.3.8 Phytonutrients

Phytonutrients, or phytochemicals (Table 12.1), are naturally occurring compounds produced by plants; they are responsible for their aroma, color, and flavor. While they have essential roles in plant growth, they also benefit human health (Rescigno et al. 2018). Phytonutrients have neuroprotective effects through different mechanisms, including antioxidant properties, anti-inflammation, apoptosis of malfunctioning cells, targeting mitochondrial dysfunction, and resolution of the abnormal accumulated and misfolded proteins (Hussain 2023; Lewis et al. 2021). With these functions in mind, and with their diverse properties and heterogeneity of constituents, phytonutrients have been explored for their potential benefits in the

Table 12.1 Phytonutrients, mechanisms of action, and examples

Phytonutrient	Mechanisms of action	Examples
Flavonoids	Antioxidant and anti-inflammatory properties Can enhance neuronal plasticity	Quercetin (found in apples and onions) Epicatechin (found in cocoa and dark chocolate)
Carotenoids	Antioxidant properties Known to promote eye health	Beta-carotene and lutein (found in carrots, tomatoes, sweet potatoes, and spinach)
Phenolic acids	Antioxidant and anti-inflammatory properties	Caffeic acid and ferulic acid (found in coffee, whole grains, berries, and spices like cinnamon)
Sulforaphane	Antioxidant and anti-inflammatory properties Can induce the expression of genes involved in detoxification processes	Found in cruciferous vegetables (broccoli, Brussels sprouts, and cabbage)

management of schizophrenia, particularly cognitive symptoms. In their extensive review, Aucoin et al. summarize various phytonutrients studied in psychosis, including preclinical and clinical studies (Aucoin et al. 2020). The latter reported positive outcomes without side effects; however, they were of small sample sizes, limiting generalizability. As phytonutrients mostly come from fruits and vegetables, this emphasizes the rationale of including fruits and vegetables in the diet of individuals with schizophrenia. Highlighted mechanisms of action in psychosis from preclinical and clinical studies included decreased inflammation and modulation of various neurotransmitters (including dopamine and glutamate) and brain-derived neurotrophic factors (Aucoin et al. 2020). So far, foods rich in phytonutrients with the best evidence to consider their use are berries, broccoli, green tea, and onions.

12.3.9 Minerals

Several studies looked at the association between different minerals and schizophrenia-spectrum disorder. While most studies primarily looked at the role of zinc in psychosis, many assessed the potential of other minerals, including copper, magnesium, and selenium. Table 12.2 briefly outlines some potential mechanisms through which minerals can be implicated in the pathophysiology of psychosis.

When looking at the levels of minerals in individuals with psychosis, three meta-analyses are relevant. One meta-analysis looked for nutritional, including mineral deficiencies, in patients with first-episode psychosis (Firth et al. 2018a). The analysis encompassed 28 studies assessing the levels of 10 dietary minerals in 480 participants (224 with first-episode psychosis, 83 with long-term schizophrenia, and 173 healthy individuals). The meta-analysis found no significant differences in any dietary mineral between individuals with first-episode psychosis and healthy individuals. Differences between those with first-episode psychosis and long-term schizophrenia did not follow a particular trend, and no studies looked at correlations between mineral levels and symptomatology (Firth et al. 2018a). The second

Table 12.2 Potential mechanisms by which various trace elements are implicated in the pathophysiology of psychosis

Mineral	Potential mechanisms implicated in the pathophysiology of psychosis
Copper	Disruption in copper transport leading to a copper-deficient state (Schoonover et al. 2020) Lower expression of copper transporters due to downregulation of dysbindin-1 expression (Schoonover et al. 2021)
Iron	Disturbances in iron biology in the prefrontal cortex (Lotan et al. 2023)
Magnesium	Intracellular magnesium deficit (Ordak et al. 2017)
Selenium	Defect in the metabolism of selenium (Berry 1993) Impact on oxidative stress through selenoproteins (Ermakov et al. 2021)
Zinc	Intracellular deficiency impacts inflammation, oxidative stress, the glutamatergic system, and the NMDA receptor activity (Petrilli et al. 2017)

meta-analysis of 33 studies looked at the concentration of various trace elements in patients with schizophrenia. The authors did not find any consistency in the pattern of variation of levels of minerals in patients and considered them unreliable as diagnostic or prognostic markers in schizophrenia. However, they noted that variations in mineral concentration can impact the onset and extent of symptomatology (Baj et al. 2020). A third meta-analysis of 39 studies with 5151 participants looked at research comparing patients with schizophrenia to healthy individuals. Results of plasma and serum data showed elevated levels of copper, along with deficits in zinc, iron, and manganese in those with psychosis compared to controls (Saghazadeh et al. 2020). The variations in the findings of the abovementioned meta-analyses can be due to the heterogeneousness of included studies, methodology, comparison groups, and assessed minerals.

Alternatively, one meta-analysis looked at the levels of zinc only in individuals with psychosis. It included ten studies, encompassing 658 individuals with psychosis and 1008 healthy controls. Results showed that the former group had significantly decreased levels of serum zinc. This was more noted among three groups: recently diagnosed, those admitted to an inpatient unit, and individuals naïve to antipsychotics (Joe et al. 2018). A population-based biomarker study looking at hair zinc levels and the risk of psychosis among antipsychotic-naïve teenagers also highlighted that decreased zinc levels might be implicated, independent of antipsychotics, in the pathophysiology of psychosis (Tabata et al. 2022).

Few studies, alternatively, assessed the role of mineral supplementation in individuals with psychosis. In their extensive meta-analysis (Firth et al. 2017), Firth et al. looked at the effects of minerals in two studies investigating Zinc (Mortazavi et al. 2015) and Chromium (Hockney et al. 2006). In the first study (n = 29), compared to placebo, zinc supplementation (150 mg/day) significantly decreased total PANSS after 6 weeks of treatment, with significant improvement in separate domains of positive and negative symptoms (Mortazavi et al. 2015). Alternatively, supplementation with either chromium (400 μg/day) or placebo (n = 100) for 12 weeks did not have a significant impact on PANSS scores (Hockney et al. 2006). The random-effects meta-analysis did not find a significant overall outcome, potentially due to the significant heterogeneity between the two studies (Firth et al. 2017). A recent 6-week trial compared zinc sulfate supplementation (220 mg every 8 h) to placebo in 88 individuals with schizophrenia. The findings showed a significant improvement favoring the experimental group on the PANSS positive and negative symptoms and psychopathology scale (Behrouzian et al. 2022). Future studies should investigate the mechanisms by which specific minerals might ameliorate symptoms of schizophrenia and identify where such supplementation could have beneficial effects.

12.4 The Role of the Immune System and Dietary-Induced Inflammation in Psychosis

An interesting aspect of schizophrenia is the role of the immune system and inflammatory markers in the development and progression of the disorder, as well as the severity of symptoms. One of the pathways implicated in the pathophysiology of schizophrenia is the peripheral immune-inflammatory pathway (Boerrigter et al. 2017). The stimulation of the immune-inflammatory response system (IRS) involves the release of proinflammatory cytokines, including interleukin 6 (IL-6), tumor necrosis factor α (TNFα), interleukin 1β, and interferon γ (Goldsmith et al. 2016). Many studies showed that psychosis is associated with an upsurge in these proinflammatory cytokines (Upthegrove et al. 2014), leading to systemic inflammation. The latter can induce microglia in the brain to release neuron-specific cytokines that affect synaptic plasticity, neurotransmitters, and cortisol concentration, which can subsequently impact mood, behavior, and cognition (Miller et al. 2009; Norden et al. 2016). Another inflammatory marker that was identified to be elevated in patients with schizophrenia is the C-reactive protein (CRP), which is triggered by IL-6 (Fernandes et al. 2016). Therefore, inflammatory markers have become indicators of the increased risk of developing psychosis (Perkins et al. 2015).

Interestingly, different states of the body can influence the immune system and, therefore, generate a risk of developing psychosis. An example of this theory would be immunological changes that occur during pregnancy and childbirth (Mor et al. 2017, 2011), wherein peripartum alterations in the immune system can explain the propensity to develop postpartum psychosis (PP) (Hazelgrove 2021). This association is supported by evidence that shows how other postpartum complications related to immune dysregulation are more likely to be found in women experiencing PP. For example, autoimmune thyroid disease (AITD) can occur due to immunological alterations during pregnancy and is particularly more prevalent in females with postpartum psychosis (Bergink et al. 2011). There is also evidence of improvement of postpartum psychotic symptoms once a woman's thyroid function returns to normal (Amino et al. 1982). Another example of how the body influences the immune system is the "stress concept" theory. The stress concept describes how stress and trauma during early childhood can lead to an elevation in inflammatory activation in the body (Pace et al. 2006). This was shown to increase the chance of developing schizophrenia afterward (Hayes et al. 2014). The inflammatory activation due to stress is also linked to prodromal symptoms and functional and cognitive impairment (Khandaker et al. 2014).

Different risk factors can cause an increased inflammatory response in patients with schizophrenia. Abdominal obesity (Manu et al. 2015), decreased physical activity (Stubbs et al. 2016), and increased smoking habits (Dickerson et al. 2017) are more likely to be found in patients with psychosis. Moreover, antipsychotics are notorious for causing weight gain in addition to altering the metabolism of lipids and glucose (Tek et al. 2016). These risk factors increase inflammatory markers in

the body, which can be used to monitor morbidity and mortality in patients with severe psychiatric illnesses, such as schizophrenia (Benros et al. 2017).

Dietary interventions have come to light as potential adjuncts for the treatment of psychosis. Diets rich in necessary nutrients can be used to reduce inflammation and metabolic disease risk (Joseph et al. 2017). For example, levels of omega-3 and omega-6 in patients with psychosis were inversely correlated with pro-inflammatory cytokines such as IL-6 (Yao et al. 2003). This highlights how an imbalance in fatty acids can be linked to changes in the IRS, which Reddy and colleagues proved to promote psychotic symptoms. Supplementing patients with fatty acids becomes a potential method of altering the IRS, decreasing IL-6 levels in the body (Reddy et al. 2004), in addition to other inflammatory markers (Hayashi et al. 1999). Clinically, this manifests as a reduction in the risk of transitioning to acute psychosis and in improvement in symptoms and social functioning (Schlögelhofer et al. 2014).

Lastly, an interesting link between diet and psychosis is found in patients living with celiac disease. When patients with celiac disease are exposed to foods containing gluten, they exhibit an elevation in the expression of HLA antigen markers on the cell surface layers of the mucosa of the intestines. These antigen markers will activate T cells and release pro-inflammatory cytokines into the bloodstream (Murray 1999). Interestingly enough, there is an increase in the incidence of celiac disease in patients with psychosis. A hypothesis is that the increased IgG response to gluten and the dysregulated immune response pathways in celiac disease are the same dysregulated pathways found in schizophrenia (Severance et al. 2012). In that regard, several case reports noted psychotic symptoms to occur in individuals with celiac disease following the ingestion of gluten (Lionetti et al. 2015). Other studies also noted that following a diet free of gluten in patients with celiac disease has improved psychiatric symptoms (Jackson et al. 2012). Therefore, it is crucial to raise awareness about the significance of cutting off gluten from the nutrition of individuals with celiac disease, particularly when they have comorbid psychiatric disorders such as schizophrenia (Kalaydjian et al. 2006).

12.5 The Gut Microbiome and Psychosis

Recently, an interaction between the brain and the gut microbiota has been attracting interest, and it is now recognized as the "gut-brain axis" (Du et al. 2020). This is a two-way communication pathway mediated by the central nervous, immune, and endocrine systems (Selkrig et al. 2014). The intestinal microbiota is the principal ecosystem in the human body and is found in the large intestine. It is populated by bacteria, viruses, fungi, and archaea (Thursby and Juge 2017). This ecosystem has been found to affect central nervous system function and behavior (Vuong and Hsiao 2017) and mental health (Valles-Colomer et al. 2019). As previously stated, it influences the central nervous system through immune and endocrine mechanisms. In addition, some microbially derived particles such as SCFA and tryptophan get

released from the intestines and reach the brain via the blood-brain barrier (Martin et al. 2018), impacting neurodevelopment.

The gut microbiota is a dynamic environment that changes with time (Caporaso et al. 2011). This change occurs due to several factors, including aging, intrinsic factors such as the immune system, and extrinsic factors like diet, medications, and stress. The intestinal microbiota also has an essential function in food breakdown and metabolism, fat storage, and monosaccharide absorption. Along the same lines, factors that affect the microbiota and its composition encompass food and nutritional status (Sandhu et al. 2017; Kovatcheva-Datchary and Arora 2013).

Clinically, neuropsychiatric disorders have been linked to changes in the gut microbiota (Huang et al. 2019). For instance, the composition of the microbiota was found to be different in individuals with schizophrenia compared to healthy ones (Nguyen et al. 2019). Dysbiosis, a disproportion or abnormality in the gut microbiota, is a known comorbidity in schizophrenia (Castro-Nallar et al. 2015) that can influence symptom severity and functioning (Nguyen et al. 2018). Patients with schizophrenia have greater intestinal permeability and greater rates of comorbidity with gastrointestinal conditions (Severance et al. 2013). The increased intestinal permeability can cause an increase of metabolites and inflammatory substances in the blood that can reach the brain and affect psychological functions (Severance et al. 2013). The gut microbiome was also linked to the severity of negative symptoms of psychosis (Schwarz et al. 2018), physical health and disease, the efficacy of psychotropic medications, and global functioning (Schwarz et al. 2018; Evans et al. 2017; Yolken et al. 2015). Besides, studies showing that probiotic treatments decrease inflammatory markers further suggest an influence of the intestinal microbiota on the IRS and the manifestation of psychiatric symptoms (Severance et al. 2017).

Since the gut microbiome is vital for the functioning of natural immunity, any dysbiosis can negatively impact the immune system and its response. This can manifest through a state of inflammation and oxidative stress, which constitutes one of the pathophysiological processes of psychiatric illnesses (Rea et al. 2019). SCFA are products of bacterial fermentation of fibers in the intestines (Miller and Wolin 1996). SCFA play a role in the IRS through their anti-inflammatory properties (Han et al. 2018) and regulation of the maturation of microglia (Erny et al. 2015). SCFAs were found to significantly decrease inflammation in psychosis (Urpi-Sarda et al. 2012). SCFA can also target dysregulated immune and epigenetic pathways in affected patients (Fan et al. 2007; Sharma et al. 2008; Song et al. 2009; Miller et al. 2011). In individuals with psychosis, the bacteria in the gut microbiota that synthesize SCFA are decreased (Karpiński et al. 2023), lowering the immune-protective characteristics of SCFA. This decrease highlights the role of dysbiosis and its impact on the immune system, which can subsequently contribute to the pathophysiology of psychosis.

Bodily enzymes can impact the pharmacokinetic and bioavailability of medications. When it comes to antipsychotics, although they are the first-line treatment for schizophrenia, they have been less than effective in 30–40% of patients (Kane 2012). Medications taken orally are usually absorbed in the gastrointestinal system,

mainly the small intestine. Any antipsychotic drug not absorbed by the stomach or small intestine arrives in the large intestine, exposing it to the gut microbiota (Li et al. 2014). The intestinal microbiome will then either activate or deactivate the drug, depending on the nature of the drug and the content of the microbiota. Studies have shown that 65% of drugs are significantly metabolized by the gut microbiome (Zimmermann et al. 2019). This suggests that it has a relevant function in drug efficacy and tolerability and, therefore, can impact a patient's treatment response. By taking into consideration the gut microbiota and its influence on drug response, it is possible to find new methods of administrating antipsychotic medications that once seemed to be ineffective, as well as discover ways to modify the intestinal microbiome to improve the efficacy of antipsychotic medications in individuals that were once considered treatment-resistant.

The gut-brain axis introduces novel avenues of treatment to be further explored in patients with schizophrenia. By learning about the gut microbiota's influence on psychotic symptoms and drug metabolism, creating interventions that can alter the gut microbiota or promoting lifestyle habits to improve it can potentially optimize the treatment received by patients.

12.6 Gluten Sensitivity in Schizophrenia Spectrum Disorders

Non-celiac gluten sensitivity manifests through gastrointestinal symptoms, including bloating, abdominal pain, fatigue, and headache (Sapone et al. 2012). Non-celiac gluten sensitivity has been associated with neuropsychiatric manifestations (Fasano et al. 2015); however, the pathogenesis of neuropsychiatric symptoms following gluten ingestion in individuals with non-celiac gluten sensitivity remains unclear. One proposed underlying mechanism is an alteration in the small intestinal barrier, followed by poor absorption of gluten peptides. These peptides cross the gut and blood-brain barriers and then bind to brain opioid receptors, causing neuroinflammation (Di Liberto et al. 2020). Another postulation relates to the autoimmune etiology of psychosis, as it was found to share several genetic features with other autoimmune diseases, such as celiac disease (Adams et al. 2012).

Historically, there are three epidemiological studies that report on the association between gluten/wheat consumption and the prevalence or incidence of schizophrenia, noting wheat intake to be positively associated with psychosis (Templer and Veleber 1980; Dohan et al. 1984; Dohan 1966). Conversely, increased gluten sensitivity has been described in schizophrenia. In one research comparing patients with recent-onset psychosis, multi-episode schizophrenia, and healthy counterparts, the first two groups had significantly elevated levels of antigliadin antibodies (Dickerson et al. 2010). Along the same lines, a recent meta-analysis of biomarkers of gluten sensitivity found that specific biomarkers are increased in individuals with psychosis. More importantly, the immunologic response pattern to gluten found in psychosis was distinct from that seen in celiac disease (Lachance and Mckenzie 2014).

Subsequently, many attempts were made to look at the function of a gluten-free diet in improving the outcomes of those with schizophrenia. A study assessing whether adherence to such a diet can be beneficial was conducted by Levinta and colleagues. The systematic review included one randomized controlled study, one open-label pilot, and seven crossover studies. The gluten-free diet was well tolerated and easy to adhere to in all studies. Six studies demonstrated its advantageous effects, particularly in decreasing the severity of symptoms and improving global functioning. The studies, however, suffered from several limitations, including heterogeneity and publication bias (Levinta et al. 2018). Following this systematic review, one pilot study of gluten-free versus regular diet in patients with psychosis positive for antigliadin antibodies showed improved negative and gastrointestinal symptoms in those who received the former diet (Kelly et al. 2019). As such, a gluten-free diet might be particularly beneficial in the subgroup of individuals with psychosis who have antigliadin antibodies.

12.7 Hunger, Eating Disorders, and Psychosis

In 2014, Seeman provided seven hypothetical explanations linking eating disorders and psychotic conditions (Seeman 2014). These are highlighted in Table 12.3.

Distinguishing between cognitions or overvalued ideas in eating disorders and delusional thinking in psychotic conditions is a daunting task due to the intricate overlap and complexities involved (Crișan et al. 2022; Veale 2002; Rahman et al. 2019).

In eating disorders, individuals often possess overvalued ideas about their body image and food, which can be intense and distressing. However, these beliefs usually remain rooted in societal influences and personal insecurities, allowing some

Table 12.3 Potential hypotheses about the comorbidity of psychotic and eating disorders

Hypothesis 1	Eating disorders and psychotic disorders are separate, but they can co-occur by chance
Hypothesis 2	Starvation in individuals with eating disorders can lead to temporary psychotic symptoms and vice versa
Hypothesis 3	Exerting control of overeating behaviors may be a response of persons at high risk, such as those with low self-efficacy, towards warding off acute psychosis. Conversely, apathy in psychosis may influence eating behaviors
Hypothesis 4	Eating disorders may share similar symptoms with psychotic disorders (i.e., body image distortions are delusions), and treating one could potentially treat the other
Hypothesis 5	Eating disorders might be an initial sign of impending psychosis or vice versa, with one condition preceding the other
Hypothesis 6	Antipsychotic medication may increase weight and induce eating disorders, while antidepressants for eating disorders might trigger psychosis
Hypothesis 7	Psychotic symptoms in eating disorders signal severity, and food refusal in psychotic illness indicates a dangerous stage with specific markers of illness severity

flexibility and responsiveness to therapy. Conversely, delusional thinking in psychotic conditions, like schizophrenia, features unyielding, irrational beliefs that remain impervious to rational arguments or evidence. The challenge arises in differentiating them, as both may exhibit strong conviction. Clinical judgment must weigh the degree of fixedness, susceptibility to counter-evidence, and the presence of other symptoms of psychosis such as hallucinations.

Alternatively, instances of bizarre eating behaviors in individuals with psychotic conditions can suggest a potential overlap between psychosis and eating disorders. However, it is crucial to approach this overlap with caution and nuance. Schizophrenia spectrum disorders can sometimes lead to unusual eating behaviors due to distorted thinking and altered perceptions of reality. These behaviors may include eating inedible objects, refusing to eat due to delusional beliefs, or adopting peculiar rituals around food (Khosravi 2021; You et al. 2021). While these actions might resemble elements of eating disorders, their origin primarily lies in psychotic symptoms rather than concerns related to body image or weight. Nonetheless, some individuals with psychotic conditions can also develop comorbid eating disorders independently, adding a layer of complexity to diagnosis. A careful, comprehensive, and typically longitudinal assessment is necessary to delineate and differentiate between the symptomatology of both conditions, allowing accurate diagnosis and the application of appropriate interventions.

12.8 Role of Diet in Physical Health Care for Psychosis

Individuals with psychosis exhibit worse physical health compared to healthy ones (Pemovska and Jovanović 2022). Several factors, including their nutrition, could explain this finding. Patients with severe psychiatric illnesses frequently adopt a poor diet, wherein they have a low intake of fruits and vegetables along with an elevated intake of fast food and sugared beverages (Teasdale et al. 2019). Likewise, patients with schizophrenia are found to ingest a greater amount of sugar and saturated fats (Ratliff et al. 2012). This increased intake of calorie-dense meals would provide one explanation for why the body mass index of individuals with schizophrenia is higher than that of unaffected counterparts (Allison et al. 1999).

Besides poor diet, individuals living with psychosis experience a decrease in physical activity. This pattern contributes to an unfavorable metabolic profile and increases the likelihood of having elevated insulin concentration, glycosylated hemoglobin, and waist circumference (Ratliff et al. 2012). They are also more likely to have higher total cholesterol, lower HDL levels, and impaired glucose tolerance (Osborn et al. 2007). These derangements contribute to a higher incidence of metabolic syndrome, which subsequently heightens the risk of developing type II diabetes mellitus, coronary heart disease, and other medical conditions (Ratliff et al. 2012). In terms of cardiovascular disease risk, such as increased blood pressure and stroke, individuals with schizophrenia are particularly at increased risk due to their increased consumption of sodium (Ratliff et al. 2012) and increased weight (Ratliff

et al. 2013). Cardiovascular risk caused by obesity is four times more substantial in patients with schizophrenia spectrum disorders compared to healthy individuals (Ratliff et al. 2013). This explains why individuals with psychosis have a 10- to 20-year shorter lifespan than the general population (Correll et al. 2022).

Another element that can affect physical health is medications. Taking antipsychotics, mainly clozapine and olanzapine, is known to contribute to metabolic syndrome through increasing appetite (Ratliff et al. 2012) and developing glucose intolerance and dyslipidemia (De Hert et al. 2011a; De Leon and Diaz 2005). Almost 80% of patients taking antipsychotics have experienced medication-induced weight gain (Green et al. 2000a). Weight adds promptly in the early period after initiating antipsychotics, although patients maintain gaining weight in the long term (Dayabandara et al. 2017). This constitutes a significant cause of medication noncompliance and relapse in patients, further worsening general health-related outcomes (Ohlsen et al. 2005). Therefore, the interplay of various factors, including unhealthy lifestyle habits and the side effects of antipsychotics, negatively impacts health outcomes and increases morbidity and mortality in individuals with psychosis (Moore et al. 2015).

Consequently, healthcare professionals should always keep in mind the physical health of their patients as part of their management plan (Carson et al. 2016). Tailoring antipsychotic medications to meet the individual's needs and regular monitoring of body mass index and other metabolic parameters are initially the most effective preventive interventions. Substituting with an antipsychotic with a lower propensity to cause weight gain is a potential possibility, but it comes with a risk of relapse of symptoms (Dayabandara et al. 2017). Regarding antipsychotic-induced weight gain, non-pharmacological approaches can help patients reduce their body mass index. Important lifestyle interventions include healthy food choices, increased physical activity, and decreased smoking (Firth et al. 2020) and have been shown to help reduce waist circumference, fasting glucose, insulin, and triglycerides levels (Bruins et al. 2014; Teasdale et al. 2017). These reductions help decrease cardiovascular risk and metabolic syndrome (Gabriele et al. 2009; Gilles and Denis 2012), as well as general morbidity and mortality (Álvarez-Jiménez et al. 2008). Nutritional counseling, exercise activities, and cognitive and behavioral therapies appear evenly efficient in individual and group formats (Dayabandara et al. 2017). One meta-analysis of nutritional interventions in individuals with severe psychiatric illnesses, including schizophrenia, found limited evidence for such strategies in correcting metabolic syndrome-related risk factors, unless they are delivered on individual basis or by dieticians (Rocks et al. 2022).

There is no substantial data to suggest routine prescription of add-on medications for weight decrease in individuals with psychosis. In that regard, multiple medications have been investigated, with metformin having the best evidence (Dayabandara et al. 2017). One meta-analysis, particularly looking at weight-loss medications licensed by regulatory bodies, concluded that the evidence is most robust for liraglutide (Lee et al. 2022).

12.9 Nutritional Interventions in Psychosis

Table 12.4 summarizes the significant meta-analyses assessing the role of nutritional supplements as adjunctive in treating schizophrenia spectrum disorders. Based on the current research, omega-3 fatty acids may be helpful in individuals in the prodrome or early stages of the disorder. High-dose B vitamins might help lessen residual symptoms in those with chronic schizophrenia. NAC may be among the most effective supplements. Results of meta-analyses are limited by the heterogeneity of trials and, in certain cases, low-quality evidence. Furthermore, the observed outcomes may be limited to subgroups with relevant genetic or dietary nutritional deficiencies.

12.10 Recommendations and Future Avenues

Schizophrenia spectrum disorders represent a complex and disabling heterogeneous group of psychiatric disorders. Current antipsychotic treatment has partial efficacy in certain groups of individuals and is frequently associated with bothersome side effects that cause medication noncompliance. In this chapter, we highlighted several possible underlying mechanisms of nutrition and dietary patterns in the etiology, development, and treatment of psychosis, including associations with specific vitamins, minerals, amino acids, and other supplements. We also discussed the roles of inflammation, the immune system, the gut microbiome, food insensitivity, and disordered eating habits in individuals with psychosis and reported on nutritional strategies that have been researched to prevent or improve symptoms. In that regard, nutritional interventions offer the potential to be adjunctive to pharmacological and non-pharmacological treatments and pose minimal risk of harm to patients. Strategies that seem to hold the most promise include NAC, omega-3 fatty acids, and certain vitamins, especially when one has a deficiency.

While examining the available research, one should keep in mind several limitations. Most of the studies on nutritional supplementation in psychosis are observational, with the majority being cross-sectional. This bounds the ability to deduce causality and the directionality of the association between unhealthy or inefficient diet and schizophrenia, an association that is likely intricate and bidirectional. The validity of data on dietary intake in individuals with psychosis can also be scrutinized, as no dietary assessment tool was validated in individuals with severe psychiatric disorders. Furthermore, several challenges in the applicability and acceptability of nutritional assessments exist in people with severe mental illness (Teasdale et al. 2020). One major challenge is cognitive impairment, a common symptom of psychosis, which hinders memory needed for retrospective assessment and prospective dietary records (Green et al. 2000b; O'Carroll 2000).

In randomized controlled trials, many factors have impeded research on diet and psychosis and might explain the ambiguous and occasionally contradictory results

Table 12.4 Summary of meta-analyses looking at the role of nutritional interventions in schizophrenia spectrum disorders

Study	Aims	Outcomes
Early interventions to prevent psychosis: systematic review and meta-analysis (Stafford et al. 2013)	To determine if pharmacological, psychological, or nutritional interventions can prevent or delay evolution to a psychotic disorder in individuals at elevated risk	– There was low-quality evidence for a positive effect of omega-3 fatty acids, compared to placebo, in preventing progression to psychosis following a 12-week course. However, the data emerged from a single trial with few participants
An update on a meta-analysis of medical and non-medical treatments of the prodromal phase of psychotic illness in at-risk mental states (Deas et al. 2016)	To investigate what would be the most efficacious treatment for individuals at high risk	– Omega 3 polyunsaturated fatty acid showed significant results in preventing progression into psychosis based on two positive trials comparing it to placebo
Efficacy of anti-inflammatory agents to improve symptoms in patients with schizophrenia: an update (Sommer et al. 2014)	To check the efficacy of anti-inflammatory molecules on symptoms of schizophrenia	– NAC showed significant effects based on one trial. – Fatty acids had no significant effect (based on seven trials; six used eicosapentaenoic and one used docosahexaenoic fatty acids)
A meta-analysis of placebo-controlled trials of omega-3 fatty acid augmentation in schizophrenia: Possible stage-specific effects (Chen et al. 2015)	To look at the effectiveness of omega-3 fatty acids at various phases of schizophrenia	– Based on ten trials, omega-3 fatty acids showed efficacy in decreasing symptoms for individuals in the earlier phases of illness (prodrome and first episode of psychosis) while having mixed findings during chronic stages of schizophrenia
Eicosapentaenoic acid interventions in schizophrenia: meta-analysis of randomized, placebo-controlled studies (Fusar-Poli and Berger 2012)	To assess the role of augmentation with eicosapentaenoic omega-3 fatty acids in treating schizophrenia and related psychosis	– Meta-analysis of seven trials concluded no beneficial effect of fatty acid augmentation on treatment
Effects of omega-3 polyunsaturated fatty acids supplements on psychopathology and metabolic parameters in schizophrenia: A meta-analysis of randomized controlled trials (Goh et al. 2021)	To investigate the efficacy of omega-3 polyunsaturated fatty acids in individuals with schizophrenia	– Based on 20 trials, omega-3 fatty acids augmentation was linked to significant improvement in psychopathology, specifically general psychopathology and positive symptoms, but not negative symptoms. – Those severely ill who were supplemented with omega-3 fatty acids containing more than 1 g of eicosapentaenoic acid per day displayed significant improvement

(continued)

Table 12.4 (continued)

Study	Aims	Outcomes
Strategies to enhance N-methyl-D-aspartate receptor-mediated neurotransmission in schizophrenia, a critical review and meta-analysis (Tsai and Lin 2010)	To examine the efficacy of molecules that enhance NMDA function on different symptoms of psychosis	– Supplementation with glycine (ten studies), D-serine (five studies), and sarcosine (five studies) significantly improved several symptom domains. – Treatment with D-cycloserine (seven studies) did not have a significant impact
Meta-analysis of the efficacy of adjunctive NMDA receptor modulators in chronic schizophrenia (Singh and Singh 2011)	To evaluate modulators of the NMDA receptor as an adjunctive treatment for schizophrenia	– The meta-analysis included 29 trials. NAC, D-serine, and sarcosine had therapeutic benefits in treating negative and total symptoms of chronic schizophrenia when used as adjuvant to non-clozapine antipsychotics. – Although glycine improved positive and total symptoms when used as an adjunct to non-clozapine antipsychotics, it worsened them when combined with clozapine
The effects of vitamin and mineral supplementation on symptoms of schizophrenia: a systematic review and meta-analysis (Firth et al. 2017)	To assess the impact of supplements on symptoms of psychosis in individuals with schizophrenia	– Pooled effects from five trials identified that vitamin B intake (including B6, B9, and B12) significantly decreased psychiatric symptoms (total symptom score) compared to the control group. – Briefer illness duration was significantly associated with superior vitamin B effectiveness. – Meta-analyses found no significant effect of B vitamins on positive (three trials) or negative symptoms (four trials). – The effect of vitamin B6 alone, as per a meta-analysis of three trials, did not reach statistical significance. – There were no benefits from antioxidant vitamins (E and C), minerals (zinc and chromium), or inositol on symptomatology

(continued)

Table 12.4 (continued)

Study	Aims	Outcomes
The efficacy of nutritional supplements for the adjunctive treatment of schizophrenia in adults: A systematic review and network meta-analysis (Xu et al. 2022)	To evaluate the efficacy of nutritional supplements as adjuncts in the treatment of schizophrenia	– Seventeen randomized controlled trials were included. – NAC was significantly more effective than vitamin B12 and omega-3 fatty acid supplementation regarding changes in the scores on the PANSS. – There were no significant differences in score changes between NAC and vitamin D supplementation. – The estimated ranking of interventions identified NAC as the most effective adjunct treatment compared to vitamin B12, vitamin D, and omega-3 fatty acids

in the literature. Besides the heterogeneity in study populations, the complexity of schizophrenia-spectrum disorders is one primary encumbering variable, wherein affected individuals have different presentations (high-risk phase, prodromal phase, acute psychosis, or chronic illness), courses of illness and relapses, treatments (which includes different types of antipsychotics with various mechanisms of action and profiles of side effects), and treatment outcomes. This complexity and heterogeneity further extend through each of the pathways that we described linking diet to psychosis. This includes the nutritional status of the individual, type of diet, baseline nutritional deficiencies, central and peripheral inflammatory reactions, the activity of the gut microbiota, the presence of particular food sensitivities, and the presence of physical or mental comorbidities. Other research limitations include the tools used to assess the abovementioned factors, such as measuring inflammation and identifying baseline gut-microbiota composition. Many of the intervention studies in the literature had the metabolic profile and physical health as primary or main outcomes, while improvement in psychotic symptoms was secondary. Therefore, there is a need for high-end quality research using specific homogenous, well-characterized populations with schizophrenia spectrum disorders.

To recruit homogenous populations, profiling participants is suggested, although it can complicate sampling and necessitate multi-site involvement. Research can also focus on population subgroups of schizophrenia spectrum disorder that may particularly benefit from dietary interventions, such as those with gluten sensitivity or baseline nutritional deficiency. Baseline study factors should be standardized, and individual characteristics should be carefully considered by analyzing confounding variables. Mental health-related outcomes should be the primary objectives. Intervention studies should be appropriately powered to identify changes in mental health outcomes. When not practical, adequately sized cohorts could be

conducted while adjusting for current food intake, psychiatric comorbidity, medications, biomarkers of inflammation, and the composition of the gut microbiome, among other potential confounding variables. To achieve the best research outcomes and unravel the complexity of this research topic, a strong network of professionals from different fields is needed (Table 12.5) (Teasdale et al. 2020).

Clinically, while the evidence collected in this chapter is inconclusive and at times contradictory, it is mainly consistent with nutritional supplements having at least some compelling latent advantage, whether preventative or therapeutic, in individuals with psychosis and being of very low risk. One should keep in mind that the probability of having a "one size fits all" dietary intervention for the management of schizophrenia is low due to multiple factors, including the heterogeneity in the pathophysiology of psychosis, its risk factors, as well as the affected individuals. A beneficial approach to incorporating nutritional interventions in treatment would be through personalized medicine, wherein nutritional psychiatry is tailored according to particular deficiencies an individual might have as per laboratory testing. This would guide any diet alteration or adjunctive supplementation for the patient and would undoubtedly benefit from the expertise of a nutritionist working with the treatment team. In that regard, many studies that showed positive outcomes of nutritional interventions in psychosis used a multimodal approach that included educational and practical workshops provided by a team of professionals, including dieticians, naturopaths, and other nutrition-informed professionals. Using a multidisciplinary team approach is necessary to implement the interventions and improve their efficacy and feasibility since experts in the field would provide them.

In conclusion, there is a robust rationale for the critical interplay between diet and psychosis. A personalized approach that involves psychiatrists, medical doctors, and mental and other health professionals is necessary while incorporating

Table 12.5 Multi-professional experts recommended to achieve the best outcomes in the field of research on schizophrenia spectrum disorders and nutritional psychiatry

Relevant stakeholders in the research on psychosis and nutrition
People who have a lived experience of a psychotic illness
Mental health professionals, particularly psychiatrists and psychologists
Dietitians or clinical nutritionists
General practitioners or family medicine physicians
Experts in implementation science
Experts in the field of gut microbiome and inflammation
Experts in preclinical and clinical research
Biostatisticians and experts in statistical analyses

nutritional psychiatry in the treatment of schizophrenia spectrum disorders. The role of nutritionists is becoming more common in that regard, not only to target physical health but also to guide a nutritional intervention when appropriate.

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Chapter 13
Effects of Coffee and Caffeine on Mood and Mood Disorders

Ahmed Radwan, Rand Akasheh, Sara Talaat, Luai Shaaban, Krishna Taneja, and Clayton Parks

Abstract Caffeine is one of the world's most frequently consumed psychoactive substances. Caffeine is widely recognized for its impact on alertness and its potential to disrupt sleep patterns. It functions as an adenosine receptor antagonist, influencing various neurotransmitters indirectly. *The Diagnostic and Statistical Manual of Mental Disorders, Fifth* Edition (DSM-5), lists four disorders directly related to caffeine intake that, aside from caffeine intoxication and withdrawal, recognize caffeine's ability to interfere with sleep and impact the level of anxiety. On the other hand, research indicates a positive impact of caffeine on neurocognitive function, particularly in conditions like Alzheimer's and Parkinson's diseases. Caffeine has been observed to enhance certain aspects of depressive disorders, such as symptoms related to amotivation. Additionally, it is commonly employed during electroconvulsive therapy to reduce seizure threshold. However, it is essential to note that caffeine usage may lower lithium levels, potentially triggering a shift to manic or hypomanic episodes in bipolar disorder. Further investigation and randomized controlled trials are imperative to fully comprehend the intricate connection between caffeine and its neuropsychopharmacologic effects.

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13.1 Introduction

Caffeine is a natural stimulant found in various plants, most commonly consumed in coffee, tea, and chocolate. This bitter-tasting compound is widely used to promote alertness and energy, with over 80% of the world's population enjoying caffeinated products daily (Petre 2020). The precise origins of human caffeine use remain mysterious, sharing a similar path to coffee and tea. Anthropologists speculate that humans discovered plants containing caffeine as early as 700,000 BCE, consuming them directly during the Paleolithic Age (Weinberg and Bealer 2001). However, the practice of infusing these plants with hot water emerged much later. Legend has it that tea was discovered in China around 2732 B.C. when Emperor Shen Nung accidentally dropped leaves into his boiling water. This chance encounter sparked a tea culture that flourished throughout the nation over the following centuries (DeWitt 2000). On the other hand, coffee's origin traces back to an Ethiopian folktale, where a goat herder named Kaldi noted the increased activity of his goats after consuming coffee berries (National Coffee Association USA n.d.). This discovery led to the creation of a coffee beverage within the local monastery, with its stimulating effects quickly spreading across the Arabian Peninsula. By the fifteenth century, coffee cultivation and trade thrived in Yemen, eventually making its way to Persia, Egypt, and other regions (Myhrvold 2021). The popularity of coffee in the Arab world gave rise to the concept of "Qahveh Khaneh," public coffee houses that served as hubs for social interaction, entertainment, and intellectual exchange (Myhrvold 2021). While historically associated with coffee and tea, caffeine's presence extends far beyond these two beverages. Today, it finds its way into various foods and drinks, including chocolate, soft drinks, and even chewing gum (Alexis 2021). In the United States, the average adult consumes approximately 135 mg of caffeine daily, which is approximately equivalent to 1.5 cups of coffee (National Coffee Association USA n.d.). Caffeine's physiological effects, namely increasing alertness and energy level, are primarily mediated by its ability to block brain receptors for adenosine, which acts as an inhibitory neurotransmitter that promotes sleepiness, increases appetite, and causes vasodilation (Baehr and Welsh 2014). This mechanism also enhances noradrenaline and dopamine activity, further enhancing feelings of well-being and motivation (Petre 2020). While moderate caffeine intake is generally considered safe for healthy adults, the FDA recommends limiting daily consumption to 400 mg (roughly equivalent to four cups of coffee daily (Petre 2020).

With the abundance of caffeinated products available, making informed choices becomes crucial. Knowing the caffeine content of various beverages and foods helps individuals manage their intake and avoid exceeding recommended limits. So in conclusion, Caffeine continues to intrigue and influence us. Understanding its

history, effects, and recommended intake empowers us to make informed choices about this ubiquitous stimulant and reap its benefits while maintaining a healthy balance (Table 13.1).

13.2 Caffeine Metabolism

Absorption and distribution: Caffeine, or 1,3,7-trimethylxanthine, is a naturally occurring alkaloid of the methylxanthine family. Possessing both hydrophilic and hydrophobic properties, it can pass easily through cell membranes and is rapidly absorbed with a rate constant (K01) of around 0.33/min (Lachance et al. 1983; Kot and Daniel 2008; Blanchard and Sawers 1983a). Notably, 99% of ingested caffeine is absorbed within 45 min of ingestion (Blanchard and Sawers 1983b), with 20% being absorbed in the stomach and the rest from the small intestine (Chvasta and Cooke 1971). The plasma concentration of caffeine peaks after 15 min to 2 h of ingestion, with this variability in peak time being attributed to delayed gastric emptying and other physiologic factors (Blanchard and Sawers 1983a). Caffeine is distributed throughout the body with a volume of 0.5–0.75 L/kg. It can reach the fetus in pregnancy and freely cross the blood-brain barrier. However, caffeine does not accumulate in any specific tissue in adult humans (Kot and Daniel 2008; Blanchard and Sawers 1983a; Fredholm et al. 1999).

Metabolism: Caffeine is metabolized through first-order kinetics via a one-compartment system model. More than 80% of caffeine is metabolized in the liver, where the CYP1A2 enzyme clears caffeine at a rate between 1–3 mg/kg/min with an elimination rate constant of 0.09–0.33/h. The action of CYP1A2 on caffeine converts most of it (84%) to paraxanthine, while 12% is converted to theobromine (a compound that also naturally occurs in cocoa), and 4% is converted to theophylline (a compound that also naturally occurs in tea). These three metabolites are further modified by the enzymes CYP1A2, CYP1A1, CYP2A6, xanthine oxidase (XO), and N-acetyltransferase-2 (NAT2) to generate various forms of xanthine, uric acid, and uracil compounds (Nehlig 2018). The metabolism of caffeine is affected by multiple factors including genetics, age, sex, pregnancy, diet, lifestyle, smoking status, environmental factors, medications, and diseases. The relationship between these factors and caffeine metabolism is summarized in Table 13.2 (Nehlig 2018).

Table 13.1 Average caffeine content of common products (Radwan et al. 2022)

Drink	Caffeine content
Brewed coffee	100 mg/6 oz cup
Instant coffee	60 mg/6 oz cup
Black tea	45 mg/6 oz cup
Green tea	20–30 mg/6 oz cup
Energy drinks	80 mg/12 oz can
Soft drinks	25–50 mg/12 oz can

Excretion: Since the renal tubules reabsorb 98% of the caffeine filtered by glomeruli, only 0.5–2% is excreted unchanged in the urine. Thus, the main limiting factor in caffeine clearance from plasma is its metabolism in the liver. While coffee consumption exerts favorable effects on the gut microbiome, it is unclear whether these effects are mediated by caffeine and its metabolites (Arnaud 2011; Nehlig 2018).

The physiological effects of caffeine: Caffeine interacts with many biomolecules, which explains its ability to convey various physiological and pharmacological functions through direct and indirect mechanisms. Importantly, it is well-accepted that caffeine exhibits most of its effects through its interaction with adenosine receptors, owing to the high structural similarity between the two compounds. The accumulation of adenosine from energy metabolism throughout the day, resulting in greater activation of its receptors, increases drowsiness and facilitates sleep onset, and caffeine's ability to block these receptors antagonizes these effects of adenosine, delaying fatigue and enhancing alertness (Lorist and Tops 2003).

13.3 Caffeine and Mood Disorders

Mood disorders encompass a spectrum of conditions, including unipolar depressive disorders and bipolar-related disorders. Both types can manifest with fatigue, insomnia, poor concentration, and decreased motivation (American Psychiatric Association 2013). However, bipolar disorders can also involve periods of excessive energy, reduced sleep needs, and increased activity levels (American Psychiatric Association 2013). Caffeine interacts with these symptoms in complex ways. Its alerting effect can contribute to insomnia, potentially worsening sleep difficulties in both conditions (Radwan et al. 2022).

- Bipolar Disorders:
- While the evidence is not conclusive, research suggests a link between excessive caffeine intake and bipolar-related mood disturbances (manic, hypomanic, and mixed episodes). This link may be particularly relevant for individuals taking lithium, a mood stabilizer commonly used in bipolar treatment. Caffeine's diuretic effect can increase lithium excretion, leading to decreased blood levels and potentially triggering relapse to episodes of mood disturbance. Additionally, caffeine's stimulating effects can impact sleep and energy levels, further contributing to episode precipitation or interfering with treatment effectiveness. Unfortunately, the authors are unable to find current treatment guidelines regarding the adjustment of caffeine intake for individuals with bipolar disorder or those taking lithium (Frigerio et al. 2021).
- Depressive Disorders:
- Fatigue, lack of motivation, and poor concentration are commonly observed symptoms of depressive disorders. Fatigue and diminished energy levels frequently emerge as the foremost symptoms reported following a depressed mood,

Table 13.2 Interindividual variability in caffeine metabolism

Factor	Impact on caffeine metabolism
Age	Caffeine clearance is slower in newborns due to immature liver function (Pons et al. 1988). Otherwise, caffeine metabolism is similar in young adults and the elderly (Blanchard and Sawers 1983a; Bonati et al. n.d.)
Sex and hormones	The main caffeine metabolizing enzyme CYP1A2 is more active in men than in women. However, this does not seem to translate into differences in urine caffeine metabolites or their ratios (Arnaud 2011). Also, the parameters of caffeine pharmacokinetics are comparable in men and women, except that the distribution volume is higher in women compared to men (McLean and Graham 2002). In women, caffeine metabolism changes through the menstrual cycle, with caffeine clearance being slower in the luteal compared to the follicular phase. While oral contraceptives do not affect caffeine distribution volume, they prolong caffeine half-life, reaching 10.6 h, especially during the luteal phase (Lane et al. 1992; Bruguerolle et al. 1990)
Pregnancy	Pregnancy slows caffeine metabolism, especially in the third trimester. Caffeine half-life is prolonged and can reach up to 11.5–18 h towards the end of the third trimester. Caffeine cannot be metabolized by the fetus or placenta, which is why its daily consumption during pregnancy can lead to its accumulation in the fetus (L. M. Grosso and Bracken 2005; Yu et al. 2016)
Dietary factors	Habitual caffeine consumption leads to partial tolerance to its effects. For this reason, caffeine consumption typically increases over time to attain the same positive/wanted effects, especially as the unwanted effects of a certain caffeine dose subsides (Nehlig 2018). Grapefruit juice decreases caffeine clearance and extends its half-life (Fuhr et al. 1993, 1995). Alcohol inhibits CYP1A2 activity and increases caffeine's half-life (Le Marchand et al. 1997; George et al. 1986). Other factors increasing caffeine clearance include broccoli and brassica vegetables (Lampe et al. 2000). On the other hand, turmeric and apiaceous vegetables (carrots, celery, parsley, caraway, fennel, etc.) decrease CYP1A2 activity (Lampe et al. 2000; Chen et al. 2010)
Obesity	The distribution volume is higher in people with obesity compared to people without obesity (Abernethy et al. 1985; Kamimori et al. 1987)
Smoking	Caffeine metabolism is enhanced, and its rate is almost doubled by cigarette smoking (Arnaud 2011). Conversely, smoking cessation reduces caffeine clearance by about 36% (Faber and Fuhr 2004). Plasma caffeine concentration may double after smoking cessation with continued caffeine consumption (Swanson et al. 1997)
Medications	Drugs that increase caffeine's half-life or decrease its clearance: oral contraceptives, some quinolone antibiotics, some antifungal drugs, the bronchodilators furafylline and theophylline, many classes of cardiovascular disease drugs, the anti-inflammatory drugs idrocilamide and rofecoxib, and the antipsychotic clozapine (Nehlig 2018). Drugs that reduce caffeine's half-life or increase its clearance: The proton pump inhibitors cimetidine, omeprazole, and ondansetron; the antidepressant fluvoxamine(Nehlig 2018)
Liver disease	In advanced liver diseases like cirrhosis, caffeine clearance is delayed, and its half-life is extended (Park et al. 2003; Scott et al. 1988)

(continued)

Table 13.2 (continued)

Factor	Impact on caffeine metabolism
Genetics	Polymorphisms in genes involved in caffeine metabolism can affect its half-life and clearance rate. Carrying polymorphisms in CYP1A1 or CYP1A2 genes is associated with habitual caffeine consumption (Sachse et al. 1999; Cornelis et al. 2006)

and they can exhibit resistance to initial treatment approaches (Asil et al. 2021). In such cases, augmenting the treatment regimen with medications like bupropion, methylphenidate, or modafinil–all of which have eugeroic and energizing effects attributed to their ability to enhance dopaminergic neurotransmission in the CNS—is sometimes done to ameliorate the residual symptoms. Caffeine is sometimes used for a similar purpose and has the ability to indirectly increase catecholaminergic activity in emotion- and reward-related brain circuits (Pandolfo et al. 2013).

- The research on caffeine and depressive disorders is mixed. Some studies suggest it may prevent depression, while others indicate it can aid in treatment (López-Cruz et al. 2018). Overall, moderate caffeine consumption (300–550 mg/day) appears beneficial for individuals with depressive disorders, but higher intake and individuals with specific neurological conditions may require caution (López-Cruz et al. 2018). Consistent with this recommendation, a systematic review with meta-analysis has found a protective effect against depression for caffeine, with an upside-down J-shaped curve dose-response relationship supporting moderate daily caffeine intake as the best strategy (Grosso et al. 2016).
- Electroconvulsive Therapy (ECT):
- Electroconvulsive Therapy (ECT) remains a well-established and effective remedy for treatment-resistant and refractory depression. Administering caffeine prior to ECT sessions is thought to improve treatment effectiveness through several mechanisms, including lowering the seizure threshold to provide a more durable response (Bozymski et al. 2018). Diverse formulations have been employed, encompassing caffeine sodium benzoate (CSB) injections (ranging from 250 to 500 mg), caffeine citrate, and theophylline, a medication with similar properties. (Bozymski et al. 2018). Oral administration can be inconsistent due to variable absorption, making parenteral routes more reliable for the desired clinical effect.

While evidence comes primarily from case reports, small trials, and retrospective studies, the use of caffeine with ECT appears safe, well-tolerated, and cost-effective (Bozymski et al. 2018). As mentioned, it may increase epileptiform activity on the Electroencephalogram (EEG) or motor seizure duration and minimize amnesia, especially for patients not achieving the desired seizure duration that might be effective for treating various psychiatric conditions (at least 30 s) (Bozymski et al. 2018).

In conclusion, caffeine interacts with mood disorders in complex ways. While it may benefit individuals with depressive disorders at moderate levels, individuals

with bipolar disorder and those taking lithium should exercise caution. Research on caffeine use with ECT is promising but requires further investigation. Ultimately, individual responses to caffeine vary, and consulting a healthcare professional is crucial for navigating its impact on mood and treatment effectiveness.

13.4 Caffeine and Psychiatric Medication Interactions

Caffeine interacts with various psychiatric medications, potentially altering their effects and necessitating careful consideration of dosing adjustment. Understanding these interactions is crucial for both healthcare professionals and individuals taking psychiatric medications.

- Impact on CYP1A2 Enzyme:
  - Competitive Inhibition: Caffeine is metabolized by the cytochrome P450 (CYP) enzyme CYP1A2. It also acts as a competitive inhibitor of this enzyme, potentially affecting the metabolism of other medications metabolized by CYP1A2 (Culm-Merdek et al. 2005).
  - Fluvoxamine: Fluvoxamine, a selective serotonin reuptake inhibitor (SSRI), also inhibits CYP1A2. This combined effect can significantly increase caffeine concentration in the blood, leading to exaggerated caffeine effects like anxiety, insomnia, and tremors (Culm-Merdek et al. 2005).
  - Smoking: The polycyclic aromatic hydrocarbons in smoked cigarettes induce CYP1A2 activity, leading to faster caffeine metabolism. This reduces the effects of caffeine and may require adjusting caffeine intake for smokers taking medications affected by CYP1A2 (Bissonnette et al. 2021).
- Serotonin Syndrome:
- Excessive caffeine intake can increase the risk of serotonin syndrome, a potentially serious condition resulting from excessive serotonergic activity in the CNS (Shioda et al. 2004). This risk can be particularly relevant when taking medications that increase serotonin levels, such as SSRIs.
- Other Medication Interactions:
  - Clozapine: Caffeine can significantly increase the plasma concentration of clozapine, an atypical antipsychotic medication, by up to 60% (Carrillo et al. 1998). This can lead to potential side effects like sedation, seizures, and increased risk of agranulocytosis (Carrillo et al. 1998).
  - Benzodiazepines: High doses of caffeine can counteract the anxiolytic and hypnotic effects of benzodiazepines, potentially reducing their therapeutic efficacy (Sawynok 1995).
  - Lithium: Caffeine's diuretic effect can increase the excretion of lithium, a mood stabilizer used in bipolar disorder treatment (Baethge et al. 2009). This can decrease lithium levels in the blood, thereby reducing its effectiveness. Conversely, abruptly reducing caffeine intake while taking lithium can lead to

abrupt increases in lithium levels, potentially causing lithium toxicity (Baethge et al. 2009). No current recommendations exist regarding the daily caffeine intake for individuals treated with lithium (Baethge et al. 2009).

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Chapter 14
Deficiencies in Vitamins and Disease-Specific Diets Impacting Mental Health

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Abstract Optimal nutrition is critical in maintaining bodily functions and preventing dysfunctions from various internal or external factors. Scientific evidence has established a strong link between dietary choices, brain health, and the risk of psychiatric disorders. Diet and nutrition significantly influence physical fitness, body composition, mood, and mental well-being through mechanisms such as reducing inflammation, acting as antioxidants, promoting neurogenesis, modifying the microbiome, and affecting the immune system. The chapter highlights the vital connection between vitamins and brain function metabolism and psychiatric conditions. Deficiencies in these essential nutrients have been associated with cognitive impairment, depression, psychosis, and other neuropsychiatric conditions. Additionally, disease-specific diets have been instrumental in mental health management. For instance, the few-foods approach benefits conditions like attention-deficit/hyperactivity disorder. Moreover, the chapter emphasizes how a well-rounded diet supplemented with vitamins positively impacts mental health, cognitive performance, and neuroinflammation. It overviews water-soluble and fat-soluble vitamins, their roles in brain metabolism, psychiatric conditions, and their impact on mental health. It discusses disease-specific diets' effects on mental well-being. It emphasizes the need for further research to comprehend the full scope of nutritional interventions in mental health improvement and outcomes. Conclusively, the chapter underscores the necessity of recognizing and addressing vitamin deficiencies, along with exploring the impact of disease-specific diets to optimize mental health. It provides valuable insights for clinicians to recognize and manage nutritional defi-

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ciencies in mental health conditions, paving the way for enhanced treatment strategies.

Keywords Vitamin deficiency · Mental health · Diseases-specific diet · Dietary intervention

14.1 Introduction

Maintaining an optimal nutritional state is crucial for keeping normal body functions and preventing or alleviating dysfunction caused by internal or external factors. Insufficient nutrition often leads to impaired function, while recommended amounts can restore or enhance body functions (Muscaritoli 2021). Increasing evidence indicates that nutrition and diet are vital for physical health and composition of the body and significantly impact mood and mental well-being. There is a connection between dietary choices and brain health, as well as the risk of psychiatric disorders. A healthy diet can influence mental health and well-being via numerous mechanisms, such as reducing inflammation, acting as antioxidants, promoting neurogenesis, modifying the microbiome and immune system, and even epigenetic modifications (Marx et al. 2017). The brain's structure and functioning, as well as the levels of hormones, neuropeptides, neurotransmitters, and the interaction between the gut and brain (microbiota-gut-brain axis), are influenced by the diet profile, consequently, play a key role in controlling stress, inflammation, and cognitive function (Adan et al. 2019). Alongside a healthy and balanced diet, supplementing micronutrients, vitamins and minerals, and macronutrients to meet their Reference Dietary Allowance (RDA) can provide additional benefits due to their diverse biological functions.

Vitamins are crucial dietary components beyond carbohydrates, fats, proteins and minerals, which are vital for sustaining life. B vitamins, for instance, are necessary for various functions, such as the production of monoamines, the synthesis of DNA, and the maintenance of phospholipids like myelin. Vitamins A, D, and E, which are fat-soluble vitamins, perform essential functions in genetic transcription, the recycling of antioxidants, and controlling brain inflammation. In psychiatric patients, vitamin deficiencies can have multiple impacts, including the development of mental illnesses and worsening symptoms. Moreover, Psychiatric symptoms can lead to poor nutrition, further exacerbating vitamin deficiencies and subclinical deficiencies, which refer to insufficient levels of vitamins without reaching clinical deficiency, which may impede patient recovery. Moreover, genetic variations can also affect the pathways involved in vitamin and essential nutrient metabolism (Ramsey and Muskin 2013).

Vitamin deficiencies have been found to impair cognition (Adan et al. 2019). Vitamin B12 deficiency, for instance, can cause fatigue and poor memory and is correlated with depression, mania and psychosis (Smith et al. 2018). Vitamin B1 deficiency leads to symptoms such as numbness and Wernicke's encephalopathy,

while Vitamin B9 deficiency has adverse effects on neurodevelopment and increases the incidence of depression in adults (Black 2008)—vitamin B3 deficiency results in pellagra and, consequently, dementia (Hegyi et al. 2004). Nevertheless, there remains a lack of clear comprehension regarding how mild or subclinical deficiencies may impact the onset of mental dysfunction (Adan et al. 2019).

Moreover, Dietary interventions can have a significant impact on brain health. One prominent example is the use of the ketogenic diet in children with epilepsy, where fasting conditions and the resulting supply of ketone bodies as an alternative energy source have been shown to reduce epileptic seizures (Neal et al. 2008). Another example is attention-deficit/hyperactivity disorder (ADHD), where a few-food approach can improve mental health (Pinto et al. 2022).

A healthy diet supplemented with vitamins has been reported to positively affect mental well-being, encompassing cognitive abilities, emotional state, stress response, and neuroinflammation. These effects have been observed in conditions correlated with elevated inflammation levels, such as liver disorders, and in elders (Firth et al. 2018). However, further research is necessary to fully understand the impact of nutritional interventions on mental well-being (Adan et al. 2019).

This chapter overviews the water-soluble vitamins (B1, B2, B3, B6, B9, B12, and C) and three fat-soluble vitamins (A, D, and E) and their role in brain metabolism and psychiatric conditions to help clinicians rapidly recognize and deal with their deficiencies. It also reviews disease-specific diets and how they impact mental health.

14.2 Overview of Vitamins and Mental Health

Vitamins are organic micronutrients that the human body needs in minor amounts (micrograms to milligrams). However, humans cannot synthesize vitamins adequately, so they consume them through diets or dietary supplements (Ramu and Neild 2018) When vitamin intake is inadequate, deficiency diseases occur.

14.2.1 Classification of Vitamins

Although grouped together as vitamins, these compounds vary chemically and can be classified into two main categories: water-soluble vitamins and fat-soluble vitamins. Water-soluble vitamins include the B complex vitamins and vitamin C. These vitamins are absorbed with food from the gut lumen to enterocytes and then to the bloodstream both actively and passively. Besides Vitamin B12, water-soluble vitamins are minimally stored in the human body. On the other hand, fat-soluble vitamins include vitamin A, vitamin D, vitamin E, and vitamin K. Opposing water-soluble vitamins, they are hardly absorbed with food but with fat. They are also stored in the liver and adipose tissue and can cause overdose and toxicity

manifestations when overconsumed in the form of dietary supplements (Ramu and Neild 2018).

14.2.2 Importance of Vitamins for Overall Health

Vitamins are crucial in maintaining the human body's physiological and metabolic states. The main two functions of vitamins are either coenzymes or antioxidants. Mostly, B complex vitamins function as coenzymes or cofactors, while vitamin C and fat-soluble vitamins function as antioxidants that react with free radicals to form stable radicals harmless to the body. More functions of various vitamins are summarized in Table 14.1 (Mason and Booth 2023), (Hanna et al. 2022), and (Rafeeq et al. 2020).

Table 14.1 Overview of the various functions of vitamins

Vitamin	Function
A. Water-soluble vitamins	
Thiamine (B1)	Cofactor in the citric acid cycle and pentose phosphate pathway Glucose metabolism and production of acetylcholine and myelin
Riboflavin (B2)	Heme proteins synthesis Synthesis of other proteins such as niacin, folic acid, and pyridoxine Carbohydrate, fat, and protein metabolism into glucose
Niacin (B3)	Is a precursor of NAD+ and NADP+, which play a key role in the electron transport chain of aerobic respiration to generate ATP and for DNA repair
Pantothenic acid (B5)	Biosynthesis of coenzyme A (CoA) that participates in cholesterol, fatty acid, and acetylcholine synthesis
Pyridoxine (B6)	Synthesis of neurotransmitters such as serotonin, adrenaline, and dopamine Immune functions by activation of immune cells and antibodies
Biotin (B7)	Glucose, fatty acids, and amino acids metabolism Cell signaling and gene regulation
Folate (B9)	Nucleic acid synthesis and red blood cell production Essential for neural tube formation
Cobalamin (B12)	Nucleic acid synthesis and red blood cell production Myelin formation and neurologic functions
Vitamin C	Antioxidant activity protecting cells against reactive oxygen species (ROS) Collagen synthesis
B. Fat-soluble vitamins	
Vitamin A	Antioxidant and immune functions—vision and light perception
Vitamin D	Calcium and phosphorus homeostasis
Vitamin E	Antioxidant function—gene expression and enzyme regulation
Vitamin K	Synthesis of blood clotting factors

14.2.3 Role of Vitamins in Mental Health and Its Physiology

Health is defined by the World Health Organization (WHO) as "a state of complete physical, mental and social well-being." Following the description of vitamins' importance in overall health, discussing the physiologic role of vitamins in mental health, which is the scope of this chapter, is essential. The role of vitamins in mental health can be attributed to their involvement in neurodevelopment, neuroprotection, neurotransmission, brain metabolism, and antioxidant functions, which are responsible for cognition and intellectuality, mood and behavior, and other aspects of mental health (Escolano-Margarit and Campoy 2018). Examples of the critical role of vitamins in the brain and mental health include:

B Vitamin Complex Thiamine (Vitamin B1) is a fundamental coenzyme in glucose metabolism, the primary energy source for the brain. It also contributes to myelin synthesis, which helps in nerve conduction. Pyridoxine (Vitamin B6) participates in the synthesis of amino acid neurotransmitters such as serotonin and adrenaline. Serotonin is known to be a mood and emotions regulator, and adrenaline is responsible for stress responses. Also, Folate (Vitamin B9) and Cobalamin (Vitamin B12) are required during pregnancy to reduce the risk of neural tube defects and proper brain myelination (Ramsey and Muskin 2013) (Escolano-Margarit and Campoy 2018).

Vitamin C has two neuropsychiatric roles in the brain. First, it is an antioxidant that prevents neuronal damage. Also, it contributes to neurotransmission by being involved in the conversion of dopamine to noradrenaline, the release of acetylcholine and catecholamines from their vesicles, and the modulation of dopaminergic and glutamatergic receptors (Escolano-Margarit and Campoy 2018).

Vitamin D is known for its role in bone growth and mineralization. However, recent studies have shown that it has receptors on neuronal and glial cells in different regions of the brain, such as prefrontal cortex, hippocampus, and substantia nigra. Also, metabolites of vitamin D are found in cerebrospinal fluid. The increasing evidence suggests that vitamin D may contribute to brain development, and its deficiency may be related to some disorders, such as depression (Escolano-Margarit and Campoy 2018).

In conclusion, vitamins have a significant role in mental health as much as in physical health, and there are more functions to discover and investigate in upcoming studies.

14.2.4 Deficiencies in Vitamins and Their Impact on Mental Health

Since the human body cannot synthesize adequate amounts of vitamins to match its needs, and the fact that most vitamins, especially most water-soluble vitamins, are not stored in the body, insufficient dietary intake leads to deficiency diseases (Ramu and Neild 2018). Those deficiencies negatively impact the mental health as well as overall health.

Vitamin deficiencies are associated with developing depression, autism, dementia, cognitive impairment, schizophrenia, and other neuropsychiatric disorders in different life stages, starting from the prenatal stage to geriatric life (Mörkl et al. 2023). The following section will describe the impact of specific vitamin deficiencies on mental health in detail.

Special Case: Pregnancy
During pregnancy, vitamin deficiencies result from both low intake and increased physiological demand. Several recent studies have focused on the effect of vitamin D status during pregnancy on postpartum depression. Postpartum depression affects up to 20% of new mothers within the first 12 months after labor. Multiple studies reported that women with low serum 25(OH)-vitamin D levels during different trimesters of pregnancy were at higher risk of reporting symptoms of postpartum depression and other mood disturbances. Other studies have reported possible associations between low levels of various vitamins, such as vitamin B9 and vitamin B12, and increasing risk of not only maternal mental disorders but also affecting delayed neurodevelopment of infants. These studies have also suggested that nutritional intervention of adequate vitamin intake during pregnancy may be beneficial for both reducing the reported symptoms by mothers and facilitating proper neurodevelopmental processes of infants (Szpunar 2020).

14.3 Vitamin Deficiency and Mental Health

Different vitamins play a crucial role in mental health maintenance, including vitamin A, vitamin B complex, vitamin C, vitamin D and vitamin E. The primary mental health condition related to vitamin deficiency is depression, which is estimated to be more than 8% of the United States affected by it (WebMD 2023) and more than 4% of the global population (Alexander A. Huang 2023). It affects all age groups, races, socioeconomic backgrounds, and ethnicities (WebMD 2023). Other mental health conditions related to vitamin deficiencies include impaired memory function, dementia, and cognitive impairment. All the vitamin deficiencies and their symptoms are summarized in Table 14.2 (WebMD 2023).

Table 14.2 Summary of vitamin deficiencies and their associated symptoms

The vitamins	Deficiency symptoms
Water-soluble vitamins	
Vitamin B1	– Memory loss, anxiety, depression, confusion, irritability and insomnia – Wernicke's encephalopathy, muscle atrophy, congestive heart failure, or even death. – Korsakoff's psychosis – The baseline vitamin B1 is linked to poor mood in women
Vitamin B2	– Depression
Vitamin B3	– Depression, apathy, anxiety, headache, disorientation, and memory loss. – In severe cases, it may lead to dementia. – Psychosis and agitation
Vitamin B6	– Stress, anxiety, fear, and psychosis
Vitamin B9	– Depression and schizophrenia
Vitamin B12	– Mood swings, paranoia, irritability, confusion, dementia, and hallucinations – Emotional liability and suspiciousness lead to violence. – Associated with autism spectrum disorders and attention defect hyperactivity disorder
Vitamin C	– Lower levels associated with depression and schizophrenia
Fat-soluble vitamins	
Vitamin D	– Depression
Vitamin E	– Associated with major depression

14.3.1 Deficiency of Water-Soluble Vitamins

Vitamin B1 (thiamine) is essential for the brain to convert glucose into energy by TPP-dependent enzymes (WebMD 2023; Dhir et al. 2019). The brain is significantly affected by thiamine deficiency as it depends on mitochondrial ATP, and thiamine plays a significant role in it (Dhir et al. 2019). So, its deficiency may cause mild neurological and psychiatric disorders such as loss of memory, anxiety, depression, confusion, irritability and insomnia (WebMD 2023; Dhir et al. 2019) or severe encephalopathy as Wernicke's encephalopathy (confusion, ataxia, nystagmus) (Ramsey and Muskin 2013), muscle atrophy, congestive heart failure, or even death (Dhir et al. 2019). Also, vitamin deficiency may lead to Korsakoff's Psychosis (confabulation, lack of insight, amnesia either retrograde or anterograde and apathy) (Ramsey and Muskin 2013). In addition, the baseline vitamin B1 is linked to poor mood in women: an improvement in its level for 3 months will improve the mood (Rao et al. 2008). Recent studies reveal that thiamine supplementation can contribute to a therapeutic approach to autism spectrum disorders (ASD) (Dhir et al. 2019).

Vitamin B2 (Riboflavin) could possibly affect mental health by its two important coenzymes, flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN) (Rouhani et al. 2023). Riboflavin is crucial in oxidative pathways, monoamine synthesis, and the methylation cycle. Although its deficiency is rare, the

marginal levels of it were found to be associated with depressed patients (Ramsey and Muskin 2013).

Vitamin B3 (Niacin) is essential in the forming process of serotonin from tryptophan. Serotonin with dopamine is considered a crucial neurotransmitter in regulating mood, so that niacin deficiency will lead to depression, apathy, anxiety, headache, disorientation and memory loss (Snyder 2020). In severe cases, vitamin B3 deficiency may lead to dementia (Snyder 2020). Also, niacin deficiency is associated with psychosis and agitation (Anderson 2003).

Vitamin B6 (Pyridoxine) has a selective modulatory effect on central serotonin and gamma-aminobutyric acid (GABA) production. GABA is a chemical messenger and inhibitory neurotransmitter found in the brain and helps block certain impulses between nerve cells, thus calming them. And so vitamin B6 deficiency will cause stress, anxiety and fear (Durrani et al. 2022). In severe cases of vitamin deficiency and due to homocystinuria, it may cause psychosis (Anderson 2003).

Vitamin B9 (Folate) deficiency is known to lower levels of S-adenosylmethionine and 5-hydroxytryptamine. The former has antidepressant properties and raises brain 5-hydroxytryptamine (5HT), which is important in mood stability. Thus, a deficiency in folic acid causes depression by affecting 5HT (Young and Ghadirian 1989). In addition, folic acid deficiency, homocystinuria and hypermethioninemia may lead to schizophrenia-like syndrome with agitation (Anderson 2003). When folate and vitamin B12 are combined as supplementation, they will enhance the production of serotonin and dopamine (WebMD 2023).

Vitamin B12 (Cobalamin) has a vital role in forming red blood cells, and its deficiency will be associated with oxygen transport problems and lead to some issues such as mood swings, irritability, paranoia, dementia, confusion and hallucinations (WebMD 2023). Additionally, teenagers with borderline vitamin B12 levels may exhibit cognitive abnormalities. In the elderly, supplementation with vitamin B12 helps enhance cerebral and cognitive functions by promoting the functioning factors related to the frontal lobe (Rao et al. 2008). In some cases, vitamin B12 deficiency may cause emotional liability and suspiciousness that lead to violence, and there are neuropsychiatric symptoms without peripheral neurological signs. In addition, the level of vitamin B12 was found to be low in autism spectrum disorders (ASD) and attention defect hyperactivity disorder (Tan et al. 2023).

Vitamin C is vital in synthesizing monoamines such as norepinephrine and serotonin, and its primary role in the brain is antioxidant. It is reported that lower levels of vitamin C are found in older people with depression and schizophrenia (Ramsey and Muskin 2013).

14.3.2 Deficiency of Fat-Soluble Vitamins

Vitamin D deficiency is a global problem affecting about 50% of the worldwide population, with one billion independent of their age and ethnicity (Guzek et al. 2021). In addition to the role of vitamin D in regulating Calcium in the blood, it has

a pivotal role in mental health through its antioxidant properties and activity in brain tissue (Akpınar and Karadağ 2022).

Vitamin E is thought to affect mental health by its antioxidant, anti-inflammatory and anti-cancer properties (Huang 2023). So, major depression is related to low levels of vitamin E, and supplementation with 15 mg/day of it will help decrease the incidence of depression (Huang 2023).

14.4 Disease-Specific Diets and Mental Health

The rate of morbidity and mortality in people with mental health diseases is consistently high. More than 318 million deaths (386.05–285.69) in 2019, with 4.92% (6.06–3.89) global disability-adjusted life-years (DALYs) due to mental health disorders (Global Burden of Disease Study 2019). Multiple factors associated with this population can explain their higher rates of mortality. It has been found that people with serious mental illnesses, especially those in advanced stages, have a higher risk of cardiovascular diseases (Shen et al. 2023), metabolic syndrome (Penninx and Lange 2018), diabetes mellitus (Mangurian et al. 2018) as well as respiratory disorders (Chiang et al. 2019). Although genetics may play a role in the physical health of these patients, environmental factors such as sedentary lifestyle, smoking, obesity, and poor diet also play a significant role (Pearsall et al. 2016).

Clinicians in the mental health field often provide disease-specific dietary advice to their patients. Although a balanced and healthy diet may have a significant role in the prevention of major diseases (Cena and Calder 2020), the efficacy of a disease-specific diet is still controversial, especially in severe mental illnesses such as Schizophrenia; thus, more randomized control trials are needed to investigate the efficacy of these disease-specific dietary programs (Pearsall et al. 2016).

14.4.1 Dietary Interventions for ADHD

In their systematic reviews of meta-analyses, researchers have investigated the effect of eliminating artificial food coloring or following a diet eliminating many foods and additives known as the few-foods diet and polyunsaturated fatty acids supplementations for children with attention-deficit/hyperactivity disorder (ADHD) (Pelsser et al. 2017). Although there is no certain evidence regarding the role of artificial food coloring elimination and polyunsaturated fatty acids supplementation in the treatment of ADHD, the role of the few-foods approach is a promising intervention for improving the mental health condition of children with ADHD, especially those who are not responsive to the medications (Pelsser et al. 2017; Hill and Taylor 2001). A few-food diet approach, such as the oligoantigenic diet, is in which the child's diet is restricted to only a few less commonly consumed foods, such as

lamb/venison, quinoa/rice, and others with low allergenic potential (Pinto et al. 2022).

14.4.2 Dietary Interventions for Depression

Anxiety and depression are recognized as the most prevalent mental health conditions in the modern world, with more than 280–301 million people living with anxiety and depression worldwide in 2019, according to a World Health Organization report. While medical treatment is the gold standard, it also has been found that both anxiety and depression increase oxidative stress and inflammatory markers within the body (Granero 2022); thus, a depression-specific regimen would include diets or supplements that are rich in antioxidants and anti-inflammatories (such as Vitamin C, Vitamin A, Polyphenol and beta-carotene) which have shown an inverse relationship with depression and anxiety severity levels (Lin et al. 2021; Kocot et al. 2017) This is particularly useful with extremes of age or medical conditions in which the medical intervention is not recommended.

14.4.3 Dietary Interventions for Autism Spectrum

Autism spectrum disorder (ASD) is a complex of symptoms that affect how children interact and communicate, impacting more than ten million children with autism worldwide and their caregivers daily (GBS 2019). Dietary interventions for autism held promising results in the improvement of symptoms of autism. Some systematic reviews and meta-analyses have shown that some interventions, such as Vitamin A supplementations and fecal microbiota transplantation, could improve behavioral symptoms in children with ASD (Yang et al. 2020; Tan et al. 2021).

14.4.4 Diet-Specific for Other Medical Conditions

The body-mind relationship is powerful. Individuals with diabetes mellitus are two to three times more likely to have depression and anxiety when compared to individuals without diabetes (Bădescu et al. 2016; Centers for Disease Control and Prevention 2023). It is also evident in patients with Cardiovascular disorders. The onset of a cardiovascular disease such as heart attack is likely to increase the risk of mental health disorders such as depression by 2.2 folds (Michal and Beutel 2021).

Given the bidirectional relationship between major medical conditions and mental health disorders, it is useful to mention special diets for some of the most common medical conditions worldwide not only to avoid direct complications and delay

the progression of the disease but also to avoid the risk of developing mental health disorders in these susceptible population.

Cardiovascular disorders are the leading cause of death worldwide, with more than 18 million documented deaths, which represents 32% of total deaths in 2019 (Global Burden of Disease Study 2019). Patients with cardiovascular disorders are advised to maintain healthy body weight as well as to follow a diet with low saturated and trans fats and high in fruits, vegetables, whole grains, and healthy sources of protein such as plant-based protein, fish, and seafood, or if lean protein, if red meat is desired (Lichtenstein et al. 2021). Additionally, there is unequivocal evidence that diabetes mellitus is preventable with a combination of physical exercise and a healthy diet (Pozzilli and Fallucca 2014). There is increasing evidence that some dietary patterns, such as the Mediterranean diet and DASH (Dietary Approaches to Stop Hypertension) diet, could help reduce the risk of diabetes mellitus in the general population. People with diabetes are also advised to maintain an active lifestyle and integrate low glycemic index food within their diet, including increasing fiber intake and reducing total and saturated fat intake (Dyson et al. 2018).

14.5 Nutritional Interventions for Improving Mental Health

14.5.1 Dietary Recommendations for Optimal Mental Health for each Age Group

Young and Mature Adults (aged 18–29 and 30 years and older, respectively) exhibit divergent mood responses based on their individual food and dietary practices. This variance is likely attributable to factors such as the level of brain maturation, age-related changes in brain morphology, and the intrinsic brain clock. The mood of young adults seems to rely on the consumption of specific foods that enhance the availability of neurotransmitter precursors and concentrations in the brain. Notably, the consumption of meat three times a week or less is associated with mental distress in young adults. However, increased meat intake possibly stimulates dopamine synthesis over time (Fernstrom and Fernstrom 2007).

Food choices, mainly fruits, influence mature adults' moods due to increased antioxidant availability. Fruits contain antioxidants that can cross the blood-brain barrier, potentially improving mood by reducing oxidative stress in the brain. Mature Adults should avoid activities that excessively activate the sympathetic system, such as drinking coffee, skipping breakfast, and consuming high glycaemic index (GI) carbohydrates. Regularly consuming breakfast in this age group may help reduce mental distress. It provides energy to the brain and helps regulate cortisol and catecholamine release associated with the fasting response (Smith 2002). Consuming breakfast regularly is associated with diminished cortisol levels and improved mental health. Conversely, skipping breakfast disrupts the natural cortisol rhythm, intensifying mental distress (Begdache et al. 2017).

Early life (from conception till the age of two) is crucial in brain development and determining vulnerability to psychiatric diseases in later stages (Adan et al. 2019). The brain needs all nutrients; however, there is an emphasis on the importance of long-chain polyunsaturated fatty acids, Vitamins A, B6, B12, and D, iron, protein, choline, folate, and iodine (Georgieff et al. 2018). For example, during embryonic development, deficiency in iodine leads to cognitive impairment later in childhood as a result of abnormal neuronal migration and irreversible damage to the cerebral cortex (Velasco et al. 2018). Breast milk supplies omega-3 and omega-6 polyunsaturated fatty acids, specifically ARA (arachidonic acid) and DHA (docosahexaenoic acid). The levels of these fatty acids in breast milk depend on the mother's diet (Oosting et al. 2015). The incorporation of omega-3 fatty acids into neuronal membranes due to a diet enriched in omega-3 fatty acids or characterized by reduced levels of omega-6 fatty acids, as evidenced by studies conducted on mice (Freedman et al. 2018; Schipper et al. 2016).

14.5.2 Supplementation and Mental Health

14.5.2.1 Supplementation in Healthy Individuals

Vitamin D There was no supporting evidence for the positive impact of vitamin D supplementation on mental health among healthy adults. It is worth noting that combining vitamin D supplementation with physical activity showed more promising results. However, other studies suggested that obtaining vitamin D from dietary sources is more effective than relying solely on supplementation (Guzek et al. 2021). Combined vitamin D and probiotics supplementation might improve mental health (Abboud et al. 2020).

Vitamin B Complex The supplementation of B group vitamins, either alone or in combination with a multivitamin, has shown potential in improving mood among both healthy individuals and those at risk of mental illnesses. However, there is a need for further investigation, particularly in at-risk populations with inadequate nutritional status or subclinical mood disturbances, to assess the efficacy of using multiple B vitamins (Young et al. 2019).

14.5.2.2 Selective Food Supplementation in the Treatment of Individuals with Psychiatric Disorders

Zinc, vitamin D, B vitamins and omega-3 unsaturated fatty acids modulate receptor degradation and synthesis, helping in synaptogenesis. They are anti-inflammatory, inhibiting apoptosis and affecting cell membrane function, BDNF action, and neurotransmitter reuptake (Mischoulon and Freeman 2013). Vitamin D deficiency is linked to an increased incidence of schizophrenia and depression (Eyles et al. 2013).

Vitamin D supplementation for 3 months, with a daily dosage of 4000 IU for the first month and 2000 IU for the following 2 months, significantly reduces the severity of depression, irritability, fatigue, mood swings, sleep difficulties, weakness, and impaired concentration in adolescents diagnosed with depression. Animal studies have confirmed this impact, showing the involvement of vitamin D in synaptic plasticity, neuroprotection, the generation of neurotrophic factors such as nerve growth factor (NGF), and the control of the dopaminergic system (Brouwer-Brolsma et al. 2016). B vitamins aid in the correct functioning of the neurological system. Folic acid (vitamin B9) deficiency has been linked to depressed symptoms in those who exhibit poor responsiveness to antidepressants (Fava and Mischoulon 2009).

14.5.3 Importance of Balanced Diet in Mental Health

A healthy diet based on whole foods can help rehabilitate and maintain mental health. Table 14.3 outlines six ways minerals and vitamins help proper brain function.

14.6 Conclusion and Future Directions

In conclusion, it is evident that vitamins play a crucial role in maintaining mental health. Deficiencies in vitamins such as vitamin B complex, vitamin C, vitamin D, and vitamin E have been associated with various mental health conditions, including depression, anxiety, dementia, and cognitive impairment. These vitamins are involved in neurodevelopment, neuroprotection, neurotransmission, brain metabolism, and antioxidant functions, which are vital for cognition, mood, behavior, and overall mental well-being.

One of the most prevalent mental health conditions related to vitamin deficiency is depression. Studies have shown that vitamin D deficiency may contribute to the development of depression. Adequate intake of vitamin D during pregnancy has also been linked to a reduced risk of postpartum depression in new mothers. Therefore, it is crucial to ensure sufficient vitamin D levels in both the general population and pregnant women.

Furthermore, vitamins B9 (folate) and B12 (cobalamin) are essential during pregnancy to reduce the risk of neural tube defects and promote proper brain myelination. Deficiencies in these vitamins can have long-lasting effects on the neurodevelopment of infants, leading to potential cognitive impairments later in life. It is imperative for pregnant women to receive adequate amounts of these vitamins through a balanced diet or supplements.

Overall, a balanced and diverse diet that includes fruits, vegetables, whole grains, lean proteins, and healthy fats is essential for providing the necessary vitamins for mental health. Supplementation may be required in cases of inadequate dietary

Table 14.3 Mechanisms of micronutrients in brain function

	Mechanism	Example
Facilitating the brain's metabolism	The metabolic processes involved in neurotransmitter synthesis and breakdown rely on micronutrients as cofactors. Because the human body cannot produce minerals or some vitamins, it is imperative to acquire them from our dietary sources	The tryptophan-serotonin pathway, a metabolic step of thousands, mandates many minerals and vitamins, e.g., iron, phosphorus, vitamin B6 etc., to work as cofactors. This is only a minor part of brain metabolism; the brain requires five distinct vitamins and seven different minerals to function properly. All neurotransmitters (GABA, adrenaline, dopamine, etc.) require the same metabolic processes (Rucklidge et al. 2021)
Mitochondrial function	Dietary factors influence the operation of both the Krebs cycle and the electron transport chain. The complexities of serotonin metabolism reflect the need for various nutrients, without a singular unique nutrient	
Modulating genetic expression (methylation)	Methylation constitutes a fundamental process crucial for gene regulation, engaging in essential functions like DNA synthesis and repair, neurotransmitter production, myelination, and immune function	As cofactors, the methylation-folate cycle depends on some nutrients, including vitamins B2, B6, and B12, to facilitate the required metabolic reactions. Increasing the availability of these nutrients has been found to have a modest impact on genome methylation, suggesting a potential influence of nutrients on gene modification. Nutrients may act as epigenetic modifiers in mental health (Stevens et al. 2018)
Anti-inflammatory function	ATP is effective against continual inflammation (Kaplan et al. 2015). As previously stated, nutrients are required to create ATP from the Krebs cycle	
Defending against environmental toxins	Poor food habits tend to enhance sensitivity to environmental toxins throughout life. A high-antioxidant diet, on the other hand, may minimize such sensitivity (Ejaredar et al. 2015)	
Enhance the concentration of brain-derived neurotrophic factor (BDNF)	The hypocaloric diet increases the concentration of BDNF and plays a role in neurodegenerative and plastic processes (Guimarães et al. 2008)	Healthy eating reduces the prevalence of depression and suicide (Lai et al. 2014; Akter et al. 2011)

intake or specific population groups with increased nutritional needs, such as pregnant women or individuals with certain medical conditions.

However, it is important to note that excessive intake of certain vitamins can lead to toxicity and adverse effects. Therefore, it is essential to follow recommended daily allowances and consult with healthcare professionals or registered dieticians for personalized nutritional recommendations.

In addition to maintaining proper vitamin levels, it is crucial to address overall nutritional status for optimal mental health. A healthy and balanced diet that includes a variety of nutrients, such as omega-3 fatty acids, antioxidants, and probiotics, has been associated with improved cognitive function, mood, and stress reactivity.

Furthermore, poor nutrition can contribute to the development and exacerbation of mental health conditions. Psychiatric symptoms can lead to inadequate nutrition, further worsening vitamin and subclinical deficiencies. Therefore, addressing both mental health and nutritional needs is critical for patient recovery and overall well-being.

Moreover, the composition, structure, and functioning of the brain are influenced by the dietary profile. The interaction between the gut and brain, known as the microbiota-gut-brain axis, plays a crucial role in regulating stress, inflammation, and cognitive function. Therefore, maintaining a healthy gut microbiome through a balanced diet rich in fiber, prebiotics, and probiotics may have beneficial effects on mental health.

Emerging Research and Future Directions To advance the development of strategies for improving mental health and preventing mental illnesses, it is crucial to gain a comprehensive understanding of the role of nutrition in pediatrics and the mechanisms involved in trans-generational epigenetic inheritance (Vickers 2014). Furthermore, the emerging field of research focusing on the gut microbiota is yielding valuable insights into key mechanistic pathways (Dash et al. 2015). These insights support the creation of specific preventive and therapeutic interventions employing dietary approaches. Considering the feasibility constraints, Randomized Clinical Trials (RCTs) will continue to be indispensable. These trials should particularly emphasize optimal dietary recommendations at both macro- and micronutrient levels. However, It is important to acknowledge that the prophylactic impact of dietary factors on mental health is likely due to the combined and synergistic effects of nutrients obtained from diverse whole-food origins, not from isolated effects of individual nutrients or food. Moreover, it is essential to emphasize that existing evidence does not support the notion that enhancing dietary practices can substitute established modalities for treating mental disorders, such as pharmacological and psychotherapeutic interventions. Rather, dietary improvement should be regarded as an approach to supplement conventional treatments and enhance overall well-being.

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Chapter 15
Ketogenic Diet, Mediterranean Diet, and Mental Health

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Abstract The role of nutrition and eating patterns in the maintenance of health and development of mental disorders has become a major focus of research over the past several decades. While key developments in pharmacotherapy and the increasing availability of evidence-based psychosocial treatments have significantly improved the survival and quality of life of those with neurological and psychiatric conditions, substantial room for improvement remains, with many individuals seeking more integrated and self-directed approaches to healing. This chapter explores the potential benefits of nutritional intervention for treating various neuropsychiatric symptoms and mental disorders by examining two well-studied dietary regimens together with their putative mechanisms for impacting emotional and cognitive health and functioning. Ketogenic diets, which typically limit carbohydrate consumption to less than 50 g daily, stimulate nutritional ketosis, which leads to adaptive changes in cellular energy utilization within the CNS; such alterations are thought to have neuroprotective and anti-inflammatory effects that have been found useful in ameliorating the derangements in glucose metabolism, oxidative stress, mitochondrial

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dysfunction, dysregulated neurotransmission, and pathologic alterations in the gut microbiome that accompany conditions like substance-related and addictive disorders, major depression, and anxiety states. Evidence suggests that a Mediterranean diet, which is marked by increased consumption of fruits, vegetables, legumes, extra virgin olive oil as a key energy source, multiple weekly servings of fish, wholegrain cereals, and fermented dairy products, together with sparing consumption of red and processed meats and avoidance of sugar-sweetened and highly-processed foods, is effective in improving metabolic and neurocognitive parameters with resulting reduced incidence of depression, improvement in sleep quality and duration, and reduction in the rate of neurological decline and development of neurodegenerative conditions such as major neurocognitive disorders due to Alzheimer's and Parkinson's disease. If additional well-designed studies in clinical populations continue to support the therapeutic benefits already demonstrated for ketogenic, Mediterranean-style, and other evidence-based healthy eating regimens, these dietary interventions have great potential not only as safer and less expensive treatment approaches but also as preventive strategies for a range of prominent medical conditions.

Keywords Ketogenic diet · Nutritional ketosis · Mediterranean diet · Addiction · Substance use disorder · Major depressive disorder · Insomnia · Alzheimer's disease · Parkinson's disease · DSM-5

15.1 Ketogenic Diet (KD) Overview

A ketogenic (or "keto") diet (KD) refers to a specialized eating regimen designed to shift the body's primary source of energy from glucose (derived from carbohydrates) to ketone body utilization. These ketone bodies, primarily beta-hydroxybutyrate (BHB), serve as an alternative fuel for the brain, muscles, and other metabolically active tissues of the body (Paoli 2014; Dowis and Banga 2021; Puchalska and Crawford 2017). The core practice of KD involves a significant reduction in carbohydrate intake, which is typically restricted to less than 50 g/day, with the remaining macronutrient content featuring high (~60%) fat and moderate (~30%) protein consumption (Volek and Phinney 2011). The significant carbohydrate restriction of KD typically necessitates limiting the consumption of common foods such as milk, yogurt, cereals, and starchy vegetables like potatoes and fruits. Moreover, any food product predominantly composed of these items or added sugars must be consumed judiciously to maintain adherence to the diet's principles (Dowis and Banga 2021). It is also essential to differentiate between the types of fats consumed on the KD. While the diet emphasizes high fat intake, the sources of these fats can significantly impact health. Unsaturated fats are typically recommended, like those found in avocados, nuts, and olive oil. Conversely, excessive consumption of saturated fats, and any intake of trans fats, should be approached with caution due to potential adverse health implications (Kolb et al. 2021).

15.2 KD Origins and Historical Significance

The use of ketogenic dietary patterns in human health and nutrition has been described since at least 500 BCE. KD began to be recognized in the 1920s as a therapeutic alternative to fasting for treating epilepsy (Ułamek-Kozioł et al. 2019). The anti-seizure effects of the diet are believed to be linked to the elevated levels of ketone bodies, reduced glucose availability, and modifications in key brain neurotransmitters (Ułamek-Kozioł et al. 2019). Over time, its potential applications have broadened, especially in treating obesity and weight management, leading to its study and adaptation for various other medical conditions (Wheless 2008; Paoli 2014).

15.3 Components of the Diet and Their Mechanisms of Action

KD's mechanism of action is believed to involve the depletion of the body's liver and muscle glycogen stores. With diminished glucose levels in the bloodstream, the body enters a fasting-like state and becomes more efficient in lipolysis as an energy source, leading to decreased appetite and weight loss for many who adhere to the diet (Paoli 2014; Puchalska and Crawford 2017). Ketones emerge from fatty acid metabolism in the liver, a process known as *ketogenesis* (Dowis and Banga 2021; Puchalska and Crawford 2017), and *nutritional ketosis* resulting from the intentional deficit in carbohydrate intake is generally defined as sustaining blood BHB levels between 0.5 and 3 mmol/L (Paoli et al. 2013). Ketosis is not just a metabolic shift but a state that offers several potential health benefits. When the body utilizes ketones for energy, it can promote enhanced fat metabolism, potentially increased energy levels, and reduced reliance on glucose. This shift can be especially advantageous for the brain, which can use ketones as a consistent and efficient fuel source, potentially leading to improved cognitive functions (Puchalska and Crawford 2017). While KD offers several advantages, it is important to note the potential risks and untoward effects. For example, some individuals might experience the "keto flu," characterized by fatigue, headaches, and mood swings, especially during the initial transition into ketosis. Additionally, long-term adherence without proper guidance and medical or nutritional surveillance can potentially result in vitamin deficiencies and electrolyte imbalances (Bostock et al. 2020).

15.4 Health Benefits of KD

KD has been associated with a multitude of potential health benefits. It has shown promise in aiding weight loss due to increased fat metabolism (Paoli 2014; Manninen 2004; Puchalska and Crawford 2017). The state of ketosis might also enhance cognitive functions and offer neuroprotective benefits, which are a topic of significant interest and have several proposed mechanisms by which KD might promote neurological health. First, ketones provide an alternative fuel source for the brain, which might lead to enhanced mental clarity and focus. Additionally, ketosis has been demonstrated to enhance the mitochondrial biogenesis of ATP and reduce the production of reactive oxygen species (ROS), potentially reducing the risk of neurodegenerative diseases and aiding in the overall health of brain cells (Bostock et al. 2020). Moreover, adherence to KD results in upregulation of polyunsaturated fatty acid (PUFA) production, which has been shown to regulate neuronal excitability by blocking voltage-gated sodium channels once PUFAs have been incorporated into the neuronal plasma membrane (Stafstrom and Rho 2012). Finally, some potential neuroprotective effects associated with KD may be driven by the established health advantages of calorie reduction, including suppression of inflammatory cytokines, decreased oxidative stress and cellular apoptosis, and increased insulin sensitivity (Maalouf et al. 2009).

By stabilizing blood glucose levels, KD can be a valuable tool for managing type 2 diabetes mellitus (Dąbek et al. 2020; Manninen 2004). However, it is strongly recommended that individuals with type 2 DM and other medical conditions consult a healthcare professional before adopting such a dietary approach. Preliminary evidence also suggests that KD could slow tumor growth and reduce chemotherapy toxicity as well as improve the quality of life for patients during chemotherapy, positioning it as a potentially complementary approach in cancer therapy (Plotti et al. 2020; Weber et al. 2020; Dąbek et al. 2020; Puchalska and Crawford 2017).

15.5 Diet Variations and True Nutritional Ketosis

While the foundational principles of KD remain consistent, interpretations and implementations can vary widely. Some adherents to the diet consume a higher proportion of carbohydrates while still targeting nutritional ketosis using alternative strategies, while others, observing that protein does not directly increase blood glucose levels, opt for a more protein-heavy version of KD (Fromentin et al. 2013). However, consuming protein in large amounts can lead to gluconeogenesis, where the liver converts amino acids to glucose, potentially hindering ketosis. The true measure of a ketogenic diet lies not just in macronutrient distribution but in the resultant production of ketone bodies (Fromentin et al. 2013). Indeed, without reaching a state of nutritional ketosis, where the body produces and utilizes ketone bodies for energy, the diet cannot genuinely be termed “ketogenic” (Puchalska and

Crawford 2017). Thus, while variations in approach can exist, the metabolic state achieved truly defines the diet and dictates health outcomes. An additional point that deserves mention is the lack of consensus and clear evidence to date of the nutritional setpoint at which ketosis occurs, which may vary significantly between individuals.

15.6 KD Relationship with Intermittent Fasting

Intermittent fasting (IF) involves cycles of eating and fasting, both of which can drive the body into ketosis. KD induces a metabolic state similar to that achieved by IF, and this state might explain the shared benefits of both diets independently (Plotti et al. 2020; Fromentin et al. 2013; Kolb et al. 2021). Moreover, the shared metabolic pathways in these two diets hint at potential synergistic health benefits when the two dietary approaches are combined.

15.7 KD and Mental Health

15.7.1 Substance-Related and Addictive Disorders

The 2021 National Survey on Drug Use and Health administered by the United States Substance Abuse and Mental Health Services Administration (Substance Abuse and Mental Health Services Administration 2022) reported that 46.3 million Americans aged 12 or older struggled with addiction to substances like alcohol and drugs (Substance Abuse and Mental Health Services Administration 2022). According to the American Society of Addiction Medicine 2011, addiction is characterized by cravings, impaired behavioral control, lack of recognition of behavioral and relational problems, and an inability to consistently abstain from a particular substance or pattern of behavior, which can include gambling, eating, Internet use, video gaming, sexual activity, and even compulsive or problematic use of mobile phones and social media (Fluyau et al. 2024). Like other diseases, addiction often involves periods of remission and relapse and can lead to early death without treatment (American Society of Addiction Medicine 2011). Since the etiology and pathogenesis of addiction are influenced by various biological, environmental, social, psychological, and behavioral factors (Fluyau et al. 2024), holistic treatment is vital to achieve the best outcomes. While addiction treatment typically focuses on psychological and pharmacological approaches, emerging research highlights the potential of dietary interventions, like KD and the Mediterranean Diet (discussed later in this chapter), to complement traditional therapies. This chapter explores how these diets interact with nutrition, brain function, and substance use to provide therapeutic benefits.

KD exerts its influence on human mental health and cognitive and emotional functioning through intricate mechanisms involving neurotransmitter modulation, oxidative stress reduction, and neuroprotection (Jang et al. 2023). As previously discussed, since KD induces a state of nutritional ketosis by suppressing insulin activity, the resulting increase in fatty acid oxidation enhances mitochondrial function, potentially mitigating oxidative damage as well as reducing inflammation (Jang et al. 2023). Ketosis also produces adaptive changes to the gut microbiome, further enhancing the anti-inflammatory effects of the diet (Santangelo et al. 2023).

Ketones have been shown to have neuroprotective effects (Jang et al. 2023), potentially mitigating neuronal damage caused by chronic problematic substance use and supporting an overall return to brain health during periods of recovery. Furthermore, ketosis leads to improved insulin sensitivity and glucose regulation (Paoli et al. 2023), which assists with treating the metabolic dysregulation associated with substance use. The stabilization of blood sugar levels and the diet's impact on balancing neurotransmitter synthesis and release also alleviates withdrawal symptoms associated with substance use disorders (Wiers et al. 2023).

Since high carbohydrate (especially sucrose) consumption is associated with pathophysiological alterations in limbic and reward-related brain circuits similar to those produced by maladaptive substance use, KD has the potential to positively influence neurotransmitter levels and activity), which play crucial roles in reward pathways, mood regulation and compulsive behaviors (Operto et al. 2020; Barañano and Hartman 2008). It also influences GABAergic and glutamatergic signaling (Barañano and Hartman 2008), which aids in reducing drug cravings and withdrawal symptoms (Wiers et al. 2023). Specifically, preclinical studies have demonstrated that habitual high sugar consumption results in an increased ratio of AMPA to NMDA-type glutamate receptors in striatal medium spiny neurons, leading to prolonged spontaneous excitatory currents causing excessive dopamine release and reduced reuptake; over time, this hyperdopaminergic state leads to reduced dopamine D2/3 as well as μ-opioid receptor availability (Fritz et al. 2018), a finding commonly associated with substance use and addictive disorders that are thought to predispose individuals to impulsive and compulsive behavior and continues to persist well into abstinence (Volkow et al. 2001; Ashok et al. 2017).

Ketones also enhance cognitive function and clarity (Jang et al. 2023), improving an individual's ability to engage in cognitive-behavioral therapy and other treatment interventions crucial for addiction recovery.

While the ketogenic diet comes with the above advantages, ketosis also results in side effects that can be disadvantageous to recovery from substance use disorders and addiction (Batch et al. 2020). The initial transition to ketosis is accompanied in some individuals by symptoms of fatigue, malaise, irritability, headache, nausea, dizziness, slowed cognition, and gastrointestinal discomfort, which collectively are sometimes termed "keto flu" or "keto-adaptation." Additionally, the diet's diuretic effect can lead to electrolyte imbalances, potentially causing symptoms like muscle cramps, weakness, and irregular heart rhythms. Another concern with prescribing KD in the setting of addiction treatment stems from the fact that people with SUD often have numerous medical comorbidities and are at increased risk for

malnutrition and gastrointestinal malabsorption (Jeynes and Gibson 2017); restricting certain food groups may further contribute to nutritional deficiencies in this vulnerable population. Since KD's insulin-suppressing effect can theoretically lead to hypoglycemia, it must be used with caution in people with diabetes mellitus. Finally, the long-term effects of KD on cardiovascular health and other aspects of the metabolic syndrome are not yet fully understood. Pregnant or breastfeeding women, individuals with certain medical conditions, or those with a history of eating disorders are recommended to adopt KD only under medical supervision. Responses to KD can vary widely among individuals, and its effectiveness likely depends on individual factors such as genetics, metabolic health, and other lifestyle modifications (Batch et al. 2020).

15.7.2 Mood and Anxiety Disorders

With Primary Psychiatric Disorder, like major depressive disorder (MDD), bipolar spectrum disorder, and schizophrenia, there is an observed reduction in high-density lipoprotein (HDL) levels (Péterfalvi et al. 2019). The course of MDD symptoms is correlated with the extent of HDL reduction (Aksay et al. 2016; Lehto et al. 2010). Conversely, KD has been demonstrated to elevate HDL levels and decrease low-density lipoprotein (LDL) cholesterol (Sharman et al. 2002; Dashti et al. 2004). Additionally, KD is associated with an increased GABA/glutamate ratio (Calderón et al. 2017), suggesting potential benefits in neuropsychiatric diseases characterized by diminished GABAergic neurotransmission and/or HDL levels; such disorders include not only epilepsy but also other neurodevelopmental conditions like autism spectrum disorder, attention-deficit hyperactivity disorder, Tourette syndrome, and schizophrenia (Deidda et al. 2014).

Research employing the Porsolt forced swim test—a model of depression-like behavior widely used in rodent studies to evaluate the antidepressant effectiveness of different therapeutic interventions—demonstrated that rats on KD exhibited increased time to immobility, indicating potential antidepressant effects (P. Murphy et al. 2004). In Balb/c mice, exercise along with KD has been shown to reduce depression and anxiety, which was associated with increased levels of beta-hydroxybutyrate (BHB) and a decreased LDL/HDL ratio (Gumus et al. 2022). Furthermore, KD is associated with reducing depressive-like behaviors in murine models of lipopolysaccharide (LPS)- and repeated social defeat stress (R-SDS)-induced depression (Guan et al. 2020). This effect was associated with the reversal of neuronal excitability induced by LPS or R-SDS and a reduction in microglial cell activation in the lateral habenula.

Gestational exposure to KD in CD-1 mice resulted in reduced depressive-like symptoms and increased sociability, indicating prolonged positive effects on the behavioral challenges associated with neurodevelopmental disorders associated with behavioral disturbances (Arqoub et al. 2020). Similarly, offspring of mice fed

KD during pregnancy were less prone to depression and anxiety, with elevated physical activity levels in utero and postnatally (Sussman et al. 2015).

Campbell and Campbell (2019) reported that 85.5% of participants with bipolar spectrum disorder experienced favorable effects of KD on mood stabilization. The same study found KD to be superior to other diets, significantly associated with higher odds of mood stabilization, reduced depression episodes, increased energy, weight loss, and improved speech coherence.

A clinical assessment of 16 adults with Parkinson's disease on KD reported alleviation of anxiety symptoms (Tidman et al. 2022).

In the context of epilepsy, the first medical condition for which KD was widely recognized to be of therapeutic value, a retrospective study at the Johns Hopkins Adult Epilepsy Diet Center revealed an association between KD duration and fewer symptoms of depression and anxiety in adults with seizure disorders (Shegelman et al. 2021). Additionally, a prospective cohort study showed a significant correlation between responder rate (defined as ≥50% seizure reduction) and higher ketone levels. However, no significant changes in anxiety or depressive symptoms were observed in this investigation. Another randomized clinical trial by (IJff et al. 2016) demonstrated that compared to the group receiving care as usual, the ketogenic diet group exhibited improved productivity and reduced anxious behavior and mood disturbances in adult epilepsy patients.

15.7.3 Other Psychiatric Disorders

The utilization of KD emerges as a potential tool in the management and treatment of several other mental disorders. A case series involving two females diagnosed with bipolar 2 disorder underscored the safety of KD management and its relative lack of adverse events (Phelps et al. 2013). Notably, the patients reported positive outcomes, including mood stabilization and symptom improvement. Another case report documented the successful application of KD in treating an elderly woman with a longstanding history of schizophrenia (Kraft and Westman 2009). The diet effectively alleviated psychotic symptoms, eliminating hallucinations that had previously triggered suicidal thoughts and contributed to unintentional weight loss.

Recent investigations, both preclinical and clinical, have highlighted the efficacy of KD in improving behaviors associated with autism spectrum disorder (ASD), observed in both mice (Ruskin et al. 2017) and children (Lee et al. 2018). These findings suggest that the benefits of KD extend across various psychiatric disorders. However, it is imperative to conduct further research in extensive clinical cohorts to thoroughly evaluate the safety and efficacy of KD in psychiatric interventions.

In summary, the literature supports the potential benefits of KD in various neuropsychiatric disorders, emphasizing the need for further research to elucidate the underlying mechanisms and optimize treatment strategies.

15.8 Mediterranean Diet

The Mediterranean diet has its origins deeply rooted in the ancient cultures surrounding the Mediterranean Sea, particularly in the Middle East (Rishor-Olney and Hinson 2024; Willett et al. 1995; Hoffman 2022). In these regions, a shared dietary pattern emerged, intertwining with their rituals, festivities, and everyday life (Guasch-Ferré and Willett 2021; Hoffman 2022). As centuries passed, these dietary practices became embedded in their cultural identity, influenced by local produce, trade, conquests, and interactions with neighboring societies (Rishor-Olney and Hinson 2024; Davis et al. 2015).

15.9 Components of the Diet and Their Mechanisms of Action

Central to the Mediterranean diet is an emphasis on whole, natural foods, ensuring the preservation of nutrient quality, which in turn promotes optimal health (Hidalgo-Mora et al. 2020). An abundant intake of fruits and vegetables supplies the body with vital vitamins, minerals, and dietary fiber, instrumental in promoting gut health and disease prevention (Rishor-Olney and Hinson 2024). Grains, mainly whole grains, provide the body with essential energy and nutrients (Lăcătușu et al. 2019; Mazzocchi et al. 2019; Rishor-Olney and Hinson 2024; Hoffman 2022).

Extra virgin olive oil, rich in monounsaturated fats and antioxidants, is a staple fat source in this diet, associated with cardiovascular health and anti-inflammatory benefits (Mazzocchi et al. 2019; Innes and Calder 2018). Fermented dairy products, especially cheese and yogurt, offer both probiotics and calcium. Fatty fish like sardines and mackerel, rich in omega-3 fatty acids (Innes and Calder 2018), are lauded for their cardioprotective and pro-cognitive benefits. The diet also advocates moderate egg consumption, as these provide a robust protein source and are rich in essential nutrients. Meanwhile, poultry offers lean protein, and red meat, consumed in moderation, provides critical nutrients such as iron (Mascitelli et al. 2014; Hoffman 2022).

15.10 Health Benefits of the Mediterranean Diet

The health benefits linked with the Mediterranean diet are extensive. Its potential to address and alleviate chronic health concerns is frequently noted in medical practice guidelines and supported by scientific evidence (Hidalgo-Mora et al. 2020). This diet not only aids in health preservation but has also demonstrated a positive impact on various chronic diseases. For instance, its high fiber content promotes optimal digestion and is linked to a reduced risk of colon cancer (Mattioli et al. 2019). Its

abundant antioxidants counter oxidative stress, delaying the aging process and decreasing the risk of various chronic and inflammatory diseases, including type 2 diabetes (Lasa et al. 2014; Esposito et al. 2015), heart disease (Widmer et al. 2015; Doménech et al. 2014), hypertension (Doménech et al. 2014), cancer (Turati et al. 2018; Schwingshackl et al. 2017), asthma (Vassilopoulou et al. 2022), and obesity (Santiago et al. 2015; Mazzocchi et al. 2019). Recent studies have underscored its potential to bolster cognitive health, with adherents showing a decreased Alzheimer's disease risk (Keenan et al. 2020). Furthermore, the diet's balanced intake of omega-3 and omega-6 fatty acids is beneficial in managing inflammation and is vital for conditions like arthritis (Picchianti Diamanti et al. 2020). It is also recognized for its role in effective weight management (Santiago et al. 2015).

15.11 Societal and Communal Aspects

The Mediterranean diet's benefits involve not only individual health and well-being; indeed, the eating practices of the diet help foster a sense of community. Meals are typically communal affairs, promoting bonding and a shared sense of belonging (Medina 2021). This social aspect, combined with the diet's emphasis on fresh, locally sourced ingredients, supports both community health and the local economy (Portugal-Nunes et al. 2021). The diet's emphasis on seasonal and local produce not only ensures fresh ingredients but also supports sustainable agricultural practices, making it environmentally friendly (Dernini et al. 2017).

15.12 Mediterranean Diet and Mental Health

15.12.1 Substance-Related and Addictive Disorders

The Mediterranean diet's potential therapeutic relevance to addiction treatment lies in its anti-inflammatory properties, which could attenuate neuroinflammation associated with substance use disorders. Additionally, the diet's focus on nutrient-dense foods could help restore deficiencies common among individuals with addictions (Davis et al. 2015).

The Mediterranean diet exerts its influence through intricate mechanisms involving neurotransmitter modulation, oxidative stress reduction, and neuroprotection. The Mediterranean diet's emphasis on polyunsaturated fatty acids and antioxidants contributes to a balanced inflammatory response and cellular resilience through microbiome modulation. These contribute to its benefits with vascular risk factors (Radd-Vagenas et al. 2018; Caracciolo et al. 2014) and benefits in addictions.

The Mediterranean dietary pattern could potentially contribute to better health and cognition by lowering the glycemic load (Rodríguez-Rejón et al. 2014),

reducing consumption of advanced glycation end products (AGEs) (Rodríguez et al. 2015), and increasing dietary fiber, omega-3 PUFAs, polyphenols (Maruszak et al. 2014), arginine (Barbour et al. 2014), and nitrates (Lidder and Webb 2013), which have been suggested to influence mechanistic pathways.

Inflammatory compounds such as interleukin-6, tumor necrosis factor-α, and C-reactive protein have been associated with the development of depressive symptoms, disturbances in neuroendocrine function, leaky gut syndrome, disrupted monoamine activity (Morris et al. 2018), and impaired overall brain function (Pano et al. 2021). Another way the Mediterranean diet favorably impacts health may be regulating the cortisol response to acute stress, suggesting that specific dietary improvements may increase stress resilience (Shively et al. 2020). Omega-3 fatty acids and polyphenols reduce inflammation and can enhance serotonin levels, potentially reducing cravings and improving mood in individuals with substance use disorders, making it a potential ally in both withdrawal and relapse prevention.

A diet rich in fiber and polyphenols fosters the growth of beneficial gut bacteria that modulate the immune system to create an anti-inflammatory response; this contributes to alleviating anxiety symptoms associated with substance use (Sadeghi et al. 2021; Foster 2021; Westfall et al. 2021; Gibson-Smith et al. 2018). Additionally, fermented food in the Mediterranean diet is rich in probiotics and prebiotics, which further help restore the gut microbiome (Abildgaard et al. 2017; Hadizadeh et al. 2019; Han and Kim 2019; Liu et al. 2020). Therefore, a fiber-rich diet assists healthy microbial growth and mitigates inflammation associated with substance use disorders. Furthermore, fiber provides a substrate for microbial fermentation. This fermentation produces short-chain fatty acids that have neuroprotective effects and contribute to a balanced gut-brain axis. Furthermore, polyphenols, vitamins, olive oil and certain fruits and vegetables are also rich in antioxidants that neutralize reactive oxygen species and combat oxidative stress, combating neuroinflammation, contributing to neuroprotection, and reducing cognitive impairments associated with addiction. The diet's anti-inflammatory properties also help reduce systemic chronic inflammation from substance use (García-Montero et al. 2021).

Furthermore, the Mediterranean diet features a relatively high intake of fruits and vegetables that are rich in vitamins and minerals that help counteract the nutrient insufficiency associated with substance use disorders, including lack of vitamin B (Malouf and Grimley Evans 2003), vitamin D (Penckofer et al. 2010), magnesium (Eby et al. 2011), and calcium (Bae and Kim 2012). Each of these nutrients regulates mood and brain function by various pathways, and thus, their adequate repletion is integral to the addiction recovery process. Nutrient supplementation can also assist with withdrawal symptoms and craving by restoring the deficiencies caused by chronic substance use and restoring the body's ability to repair itself (Penckofer et al. 2010).

15.12.2 Mood Disorders

There is evidence suggesting that adopting a Mediterranean-style dietary pattern may decrease the risk of depression. A Mediterranean-style dietary intervention, encompassing cooking classes, provision of food hampers, and fish oil supplementation (900 mg/day docosahexaenoic acid [DHA] and 200 mg/day eicosapentaenoic acid [EPA]), demonstrated enhanced adherence to the Mediterranean diet, leading to reduced depression and improved mental health-related quality of life (Parletta et al. 2019).

Contrarily, a recent meta-analysis found no discernible difference in the incidence of depression between individuals with the highest and lowest adherence to the Mediterranean diet (Li et al. 2017; Rienks et al. 2013). These discrepancies might be attributed to variations in methodology or clinical diversity across studies. Additionally, it is crucial to acknowledge that the prevalence of the Mediterranean diet is higher in regions with increased sun exposure, milder climates, and longer daylight hours—factors historically associated with improved depression outcomes, thus introducing a potential confounding element (Abraham et al. 2021; Murphy and Parletta 2018) Consequently, the ongoing discussion on the relationship between the Mediterranean diet and depression remains open to further exploration.

15.12.3 Insomnia and Other Sleep Disorders

The correlation between diet and sleep is well-established, with an imbalanced diet potentially having adverse effects on both the quality and duration of sleep. Conversely, maintaining a healthy diet can positively impact sleep parameters. Not only the type of food consumed but also the eating patterns and timing of meals play a role in influencing sleep. Adopting an overall healthy lifestyle by modifying dietary habits proves more effective in enhancing sleep quality and efficiency than isolated changes to specific nutrients or foods.(Scoditti et al. 2022).

Scientific evidence suggests that the Mediterranean diet, characterized by a moderate-to-high intake of fruits, vegetables, nuts, olive oil, wholegrain cereals, and fish, may promote better sleep. The Mediterranean diet contrasts with a typical Western diet by the former featuring low consumption of red meat, saturated fat, and sugary foods, which are associated with negative impacts on sleep quantity and quality, including insomnia (Oliveira and Marques-Vidal 2023). Olive oil, a staple of the Mediterranean diet, is particularly noteworthy for its potential to provide monounsaturated fatty acids (MUFAs) and polyphenols, offering potential protective effects for sleep. Recent studies highlight the positive association between the consumption of fatty fish, a significant source of omega-3 PUFAs such as DHA and EPA, and longer sleep duration with earlier sleep onset (Dinu et al. 2018).

The link between diet and sleep involves the modulation of the tryptophan-serotonin-melatonin system. The Mediterranean diet, rich in melatonin precursors

like tryptophan and serotonin, as well as melatonin itself, aids in promoting sleep. Additionally, the diet facilitates the transportation of tryptophan across the blood-brain barrier (BBB). Nutrients such as n-3 fatty acids and B-group vitamins found in the Mediterranean diet contribute to melatonin biosynthesis in the brain (Schwingshackl et al. 2020).

Polyphenols, natural antioxidants abundant in the Mediterranean diet, play a role in sleep regulation. While some studies on polyphenol supplements yielded inconsistent results, the overall antioxidant potential of the diet, measured as total antioxidant capacity (TAC), has been linked to a reduction in sleep problems. The Mediterranean diet's anti-inflammatory and immunomodulating effects distinguish it from Western or low-fat diets. By downregulating inflammatory markers, the diet exerts beneficial effects on sleep. Furthermore, the diet's potential for weight loss, especially in normal or slightly overweight individuals, may contribute to improved sleep quality, possibly due to metabolic factors.(Guasch-Ferré and Willett 2021).

The Mediterranean diet's impact on vascular function, particularly endothelial function, is crucial. Sleep disturbances can lead to endothelial dysfunction, potentially causing atherosclerosis and cardiovascular diseases. The diet's positive influence on endothelium function contributes to regulating sleep and preserving brain function, as evidenced by improvements in plasma concentrations of brain-derived neurotrophic factor (BDNF) (Trichopoulou et al. 2014).

15.12.4 Neurocognitive Disorders

The aging population's health challenges, particularly cognitive impairment and dementia, have garnered significant attention due to their social, economic, and medical impact. Currently, there is no cure for most conditions leading to cognitive decline, emphasizing the importance of preventive strategies and lifestyle changes, with a focus on adopting a healthy diet. The Mediterranean diet, characterized by a high intake of fruits, vegetables, cereals, legumes, and olive oil, along with low consumption of saturated fats and moderate alcohol intake, has been shown not only to improve cognitive function but also to reduce the risk of age-related medical comorbidities such as stroke, type 2 diabetes, and cardiovascular disease—all conditions that influence cognitive health.(Petersson and Philippou 2016).

Numerous studies indicate that adhering to the Mediterranean diet can slow down cognitive decline and decrease the risk of Alzheimer's disease and dementia, as assessed through cognitive function tests. The complex relationship between nutrition and brain aging involves factors such as reduced blood flow, inflammation, the accumulation of reactive oxygen species, β-amyloid, neurofibrillary tangles, and protein tau.(Lourida et al. 2013).

The Mediterranean diet's positive impact on cognitive function and dementia risk reduction is attributed to various mechanisms. It has been associated with enhanced endothelial function, improved cerebrovascular blood flow, and documented antioxidant and anti-inflammatory properties. Certain nutrients in the

Mediterranean diet, such as MUFAs and polyphenols, contribute to microvascular endothelial improvement. Additionally, the diet plays a role in ameliorating hypercholesterolemia, controlling serum lipid profiles, reducing atherosclerotic plaques, and improving blood flow. The rich vitamin and polyphenol content of the Mediterranean diet provides neuroprotective effects, reducing oxidative stress biomarkers and positively influencing cognition.(Petersson and Philippou 2016).

The Mediterranean diet's emphasis on omega-3 PUFAs is beneficial for brain development and optimal neurological function. Studies demonstrate that omega-3 PUFAs can decrease neuroinflammation, positively upregulate neurotransmission processes, and exert neuroprotective effects against various cerebral conditions. Polyphenols in the diet, including flavonoids, resveratrol, and hydroxytyrosol, exhibit neuroprotective actions by safeguarding neurons, brain capillaries, and endothelial cells against inflammatory stimuli, oxidative stress, and protein aggregates. This contributes to a reduction in β-amyloid pathology and tau protein aggregation, which are characteristic features of neurodegenerative disorders. Moreover, polyphenols may enhance synaptic plasticity, improving cognitive parameters such as memory and learning. The high intake of micronutrients like vitamins C, E, B, folate, flavonoids, and carotenes associated with the Mediterranean diet has been linked to a decreased risk of aging-related cognitive decline and the development of major neurocognitive disorders (Scoditti et al. 2022).

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Chapter 16
Myths About Diet and Mental Health

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Abstract Recently, the relationship between nutrition and mental health has gained considerable scientific interest. In this chapter, we aim to highlight and disentangle myths about diet and various psychiatric conditions that have often clouded public understanding. We systematically examine a range of popular beliefs that pertain to diet and its relationship with psychiatric conditions, including eating disorders, mood disorders, and psychosis. We then review the literature on the role of particular food types and diets in mental health. While tackling each of the above, we carefully debunk misconceptions by focusing on evidence-based research and clinical data. In pointing out fallacies, we emphasize the critical interplay between diet and mental health, with the former operating as a constituent in a more complex matrix of factors. Our review concludes with clinical recommendations that guide how best to utilize dietary nutrients in promoting mental health.

Keywords Nutrition · Diet · Mental health · Myths · Misconceptions

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16.1 Introduction

Nutritional psychiatry is a novel yet flourishing field in mental health, playing a promising role in the prevention and treatment of psychiatric conditions. Systematic reviews conducted in this domain show that healthy dietary patterns tend to be inversely related to the risk of developing psychiatric outcomes, such as depression and anxiety (Lai et al. 2014; O'Neil et al. 2014). Some of the biological mechanisms that are moderated by diet include inflammation, oxidative stress, brain plasticity, microbiota-gut-brain axis, and mitochondrial dysfunction (Marx et al. 2017). Understanding these complex mechanisms has promoted clinical research that introduced the incorporation of dietary and nutritional supplements in the treatment of both common and severe psychiatric disorders (Jacka et al. 2017; Sarris et al. 2009).

Various advances have indeed been made in the field linking nutrition to neuropsychiatric outcomes. Symptoms of anxiety and depression, for example, have been positively correlated with highly processed foods, but negatively correlated with the Mediterranean diet (Jacka et al. 2012). A diet rich in sugar, salt, and fat, strongly linked to obesity, has been indirectly yet positively associated with the risk of dementia, particularly Alzheimer's disease (Naderali et al. 2009). For instance, in one 27-year longitudinal study, obesity in middle-aged individuals increased their risk of dementia, independently of other comorbid conditions (Whitmer et al. 2005).

However, recent studies in nutritional psychiatry started to scrutinize the bidirectional influence between gut microbiota and the brain, which affects neurocircuitry and behavior (Carding et al. 2015). Research has highlighted the effect of diet on the neurogenesis of the hippocampus, a brain region responsible for learning, memory, and mood (Stangl and Thuret 2009).

As nutritional psychiatry is a new avenue of treatment that mental health professionals, clinicians, nutritionists, and researchers are actively exploring and trying to fully understand, conflicting evidence concerning the role and efficacy of nutritional and food-related interventions is bound to exist. This has paved the way for the dissemination of information that has been shown as preliminary or unreliable, resulting in the occurrence of various related misconceptions.

The purpose of this chapter was to dissect the common misconceptions and myths in the field of nutritional psychiatry. We start by exploring the intricate relationship between nutrition and various eating disorders (EDs), with a particular focus on anorexia nervosa and bulimia nervosa. We then look at the role of diet in other various neuropsychiatric conditions, mainly autism, mood disorders, psychosis, and addiction. We debunk these myths and present an updated review of evidence-based correlational relationships between diet and different mental health symptoms and diagnoses. We highlight the role of particular food types, diets, and lifestyles in mental health; we particularly focus on red meat, dairy products, tea, ketogenic diet, gluten-free diet, and Paleolithic diet. We conclude with recommendations that guide how best to utilize dietary nutrients in promoting mental health.

16.2 Eating Disorders

EDs encompass a range of conditions that can significantly affect the psychological, physical, and social aspects of an individual's life. They usually revolve around a preoccupation with food, body dissatisfaction, and distress associated with controlling body shape (Hay 2020). According to the fifth edition of the Diagnostic and Statistical Manual (DSM-5-TR), feeding and EDs include bulimia nervosa, anorexia nervosa, binge eating disorder, pica, rumination disorder, avoidant/restrictive food intake disorder, and other specified and unspecified feeding or eating disorders (American Psychiatric Association 2022). A recent systematic review suggested a lifetime prevalence of 0.9% and a 1-year prevalence of 0.43% of EDs (Qian et al. 2021). Bulimia nervosa, binge eating disorder, and anorexia nervosa are the most common disorders with prevalence rates of 2.4–2.6% (Bagaric et al. 2020; Silén et al. 2020; Stice et al. 2013), 1.4% (Fangueiro and Colombo-Souza 2023), and 0.5–0.9% (Favaro et al. 2003; Hudson et al. 2007) in the general population, respectively. Many misconceptions cloud the public's—and sometimes the scientific—perception of EDs, their etiologies and causes, prevalence, and treatment. In this section, we tackle major myths about EDs, including the body characteristics of affected individuals, gender differences in prevalence and causes, available treatments, and comorbidities.

16.2.1 Myth 1: Individuals Diagnosed with Eating Disorders Are Underweight

Social media has popularized a slender body ideal for women and a more muscular figure for men. This stereotype has been associated with an increase in body dissatisfaction, particularly among adolescents (Dhoke et al. 2023). A common related misconception is that EDs only revolve around extremely low weight and severe thinness. However, in reality, weight varies among individuals with EDs. Disordered eating behaviors result in either deficient or excessive food consumption, which can cause weight fluctuation (Rikani et al. 2013). According to the DSM-5-TR, anorexia nervosa is the sole ED that requires the patient to be significantly underweight as part of its diagnostic criteria. A significantly low body weight, as measured through the body mass index (BMI), is defined as a weight lower than expected in terms of age, sex, and physical well-being. A BMI value helps to specify the severity of anorexia as mild (17–18.5 kg/m^2), moderate (16–16.99 kg/m^2), severe (15–15.99 kg/m^2), and extreme (<15 kg/m^2) (American Psychiatric Association 2022).

On the other hand, those with bulimia nervosa and binge eating disorder remain within normal weight range or overweight. An epidemiological study conducted in 2008 concluded that only 3.5% of those diagnosed with bulimia and none of those with binge eating disorder were underweight (Hudson et al. 2012). Bulimia nervosa is identified by a pattern of binge eating and subsequent compensatory behaviors to

prevent weight gain. Compensatory behaviors range from vomiting to the use of laxatives. Alternatively, binge eating disorder occurs when an individual has recurrent episodes of marked overeating. The quantity of food consumed is noticeably high within a brief period (American Psychiatric Association 2022). Considering the wide variety of EDs, their presentation, and epidemiology, normal body weight or BMI should never preclude assessment for or provision of a diagnosis of ED.

16.2.2 Myth 2: Eating Disorders Only Occur in Females

A common misconception about EDs is that they only occur in females. This has stemmed from the discrepancies in prevalence between the two genders. The lifetime prevalence of anorexia nervosa reaches up to 4% in females, compared to 0.3% in males. The same trend is observed in bulimia nervosa whose lifetime prevalence is 3% in females and 1% in males (van Eeden et al. 2021). When it comes to binge eating disorder, lifetime prevalence is also higher in females (0.6–6.1% compared to 0.3–0.7% in men) (Silén and Keski-Rahkonen 2022). However, despite higher rates in females, recent evidence suggests that the prevalence of EDs is more rapidly increasing in males (Gorrell and Murray 2019).

A recent commentary has drawn attention to the issue of gender discrepancies in research on EDs. It is estimated that less than 1% of studies on EDs have exclusively focused on male presentations (Murray et al. 2018). This lack of empirical evidence has contributed to the misconception that disordered eating behaviors are rare among males. Consequently, major clinical trials continue to exclude males from their study samples and mainly focus on female patients. This bias could significantly impact the course of treatment for males with EDs, potentially hindering their access to mental health services (Murray et al. 2018). It is also important to highlight that this gender discrepancy previously extended to clinical grounds. The DSM-IV contained a gender-biased criterion for anorexia nervosa, notably criterion D which stated: "In menstruating females, absence of at least three consecutive non-synthetically induced menstrual cycles" (American Psychiatric Association 1994, 2022; Andersen 1990). This criterion had no equivalent symptom for male patients. It was subsequently removed from the DSM-5 due to its lack of clinical utility and to emphasize that anorexia nervosa is an inclusive disorder that can affect individuals of all genders (Attia and Roberto 2009; Dalle Grave et al. 2008).

Spratt and colleagues discuss in detail EDs in men and the unique challenges they usually face (Spratt et al. 2022). Identification of ED symptoms in males could be more difficult as research suggests that the presentation might differ between genders (Murray et al. 2017). Indeed, the majority of male individuals suffering from EDs are categorized as having a DSM diagnosis of "Eating disorder not otherwise specified," suggesting that typical disordered eating behaviors and patterns do not regularly present in males (Le Grange et al. 2012). Gender differences in the perception of the ideal body shape and image could affect the manifestation and detection of these symptoms. For example, while such perception typically revolves

around thinness-oriented thinking and behavior patterns in females, it often centers around masculinity and a muscular body in males (Murray et al. 2017). As a consequence, behaviors exhibited by the two genders to "reach" the ideal body shape might differ. It is also important to keep in mind that psychometric measures used to detect EDs have been validated only in females (Darcy et al. 2012). Furthermore, help-seeking rates are low among men with EDs, and delayed treatment is often observed (Bomben et al. 2022). All of the above factors have interfered with males with EDs being diagnosed and receiving the appropriate help they need. For further readings on this topic, Breton and colleagues provide a comprehensive review of the role of sex and gender in EDs, along with recommendations for gender and sex considerations in guiding clinical practice and advancing ED research (Breton et al. 2023). Huckins and colleagues extended their discussion beyond gender and highlighted EDs as conditions that can "affect people of all genders, ages, races, ethnicities, body shapes and weights, sexual orientations, and socioeconomic statuses" (Huckins et al. 2022).

16.2.3 Myth 3: Eating Disorders Are a Choice

Most individuals living with a mental health condition struggle with associated stigma. This can lead to the belief that having a psychiatric disorder or symptoms is a choice that the individual makes to gain sympathy or other gains (Corrigan and Watson 2002). From this perspective, a prevalent stigmatizing belief centers on individuals with EDs bearing responsibility for their symptoms and their overall condition. An investigation into the stigma surrounding EDs revealed that over a third of the study participants attributed blame to individuals with EDs, irrespective of the subtype of the disorder, believing that they could overcome their condition if they so desired (Crisp et al. 2000). Thompson-Brenner et al. (2012) found that even healthcare practitioners held such a belief of having the choice in stopping or controlling the ED. A recent scoping review of 46 studies concluded that stigmatization against EDs negatively impacted affected individuals, their psychological well-being, and treatment-seeking behavior (Brelet et al. 2021). The authors raised their worry that stigmatization of EDs increases the risk of developing an ED or maintaining an already existing one (Brelet et al. 2021).

EDs are complex multilayered conditions influenced by biopsychosocial factors, with genetic and environmental variables playing integral roles. Psychological and environmental factors influence genetic predisposition, subsequently contributing to the development of EDs or ED symptoms (Culbert et al. 2015). One meta-analysis showed that exposure to media portraying the ideal thin body figure resulted in changes in eating disorder symptoms, particularly among individuals at high risk for developing an ED (Hausenblas et al. 2013). Genetic factors play a major part in both anorexia nervosa and bulimia nervosa, with an estimated heritability rate of 50–83%. These estimates are based on twin studies discussed in Klump et al. (2000) review of the available literature. Other risk factors for developing disordered eating

symptoms include physical illnesses, personality factors, peer context, childhood bullying, and stressful life events (Keel and Forney 2013; Lie 2022). It is important to investigate relevant risk factors when assessing an affected individual's condition and planning appropriate interventions.

16.2.4 Myth 4: Eating Disorders Cannot Be Treated

Multiple treatment modalities are available for managing EDs (Grenon et al. 2019). Typically, treatment is comprehensive and multidisciplinary, encompassing more than one type of intervention. The treatment team includes a psychiatrist, psychologist, social worker, general practitioner, nutritionist, and case manager, among other team members (Halmi 2005).

Several psychotherapeutic models have been developed to target EDs. Specifically, cognitive behavioral therapy-enhanced (CBT-E), interpersonal psychotherapy-eating disorders (IPT-ED), and group therapy for EDs are used (Fairburn 2008; Grenon et al. 2017; Rieger et al. 2010). A meta-analysis looking into the outcomes of psychological interventions for EDs concluded that the long-term efficacy for AN, BN, and BED was 49%, 44%, and 45.5%, respectively. Overall, no treatment was deemed superior for AN, and both CBT and IPT were found to be equally effective for BN and BED (Kass et al. 2013).

Pharmacological interventions can help treat bulimia nervosa, binge eating disorder, and comorbid disorders such as depression and anxiety (Davis and Attia 2017; Hay and Claudino 2012). Fluoxetine and dexamphetamine are approved by the FDA for the management of bulimia nervosa and binge eating disorder, respectively (Food and Drug Administration 2021). In anorexia nervosa, a systematic review suggested olanzapine as the treatment most frequently prescribed. International guidelines also propose using it and aripiprazole in clinically severe or treatment-resistant situations (Thorey et al. 2023). Several meta-analyses also showed a beneficial effect of deep brain stimulation in treatment-refractory anorexia nervosa (Hsu et al. 2022; Karaszewska et al. 2022; Shaffer et al. 2023). Unfortunately, due to the stigma around EDs and barriers to treatment, only about 23% of those with active ED symptoms receive treatment (Griffiths et al. 2018). The most substantial barriers to treatment include one's fear of losing control, fear of change, and difficulty finding motivation to change (Griffiths et al. 2018).

16.2.5 Myth 5: Eating Disorders Are Isolated Conditions

More often than not, EDs are associated with high psychiatric comorbidity. Up to 70% of those with an ED have at least one mental health comorbidity (Keski-Rahkonen and Mustelin 2016). The most common comorbidities are anxiety disorders (65%), depression (32–50%), obsessive-compulsive disorder (15–19%), and

SUDs (21.9%) (Bahji et al. 2019; Hudson et al. 2007; Keski-Rahkonen and Mustelin 2016; Speranza et al. 2001). In anorexia nervosa, a 2-year longitudinal study looking at the outcomes of adolescents aged 14–18 years who met the diagnosed criteria for the disorder concluded that those suffering from anorexia nervosa have an increased risk of developing another psychiatric disorder, even after recovery from anorexia (Halvorsen et al. 2004). Along the same lines, a recent review looking at psychiatric comorbidities in anorexia noted high comorbidity with various psychopathologies, specifically mood and anxiety disorders, obsessive-compulsive disorder, and personality disorders (Marucci et al. 2018). The authors highlighted the importance of an extensive psychological, somatic, and nutritional assessment of these individuals to develop an appropriate multidisciplinary treatment plan (Marucci et al. 2018). Bulimia nervosa is frequently associated with substance misuse, with alcohol and substance dependence rates reaching 46% (Bulik et al. 2004). Data extracted from the Swedish Twin Registry noted that females with EDs have a range of substance use behaviors, particularly observed in anorexia nervosa and comorbid anorexia and bulimia (Root et al. 2010). This is of clinical relevance as a retrospective cohort study showed that, in comparison with matched controls, SUDs (alcohol, cannabis, and hard drug misuse) had an additive negative effect on all-cause mortality risk in individuals with EDs (Mellentin et al. 2022). A recent meta-analysis looking at comorbidities in binge eating disorder highlighted the high co-occurrence of the disorder with obesity, type 2 diabetes, and hypertension. Additionally, it noted comorbidities with psychiatric disorders including mood disorders (70%), SUDs (68%), anxiety disorders (59%), and post-traumatic stress disorder (32%) (Keski-Rahkonen 2021).

16.3 Nutrition and Other Mental Health Conditions

16.3.1 Autism Spectrum Disorder

Autism spectrum disorder (ASD) is a multicomplex disorder characterized by a range of specific symptoms in social communication, restricted interests, and repetitive behaviors (American Psychiatric Association 2022) ASD occurs worldwide, and its incidence is estimated to be higher than 1 in 100 individuals (Maenner et al. 2020). The causes of ASD are related to genetic predisposition, early brain development, and environmental influences (Chaste and Leboyer 2022).

Many attempts have been made to find a connection between nutritional deficiencies, such as vitamin D and folate, and autism risk. However, most of these studies are limited due to their inability to evaluate the deficiency before an autism diagnosis is made (Modabbernia et al. 2017). A meta-analysis of the association of vitamin D with autism found that people with autism had much lower serum 25-hydroxy vitamin D levels than people without ASD (Wang et al. 2016). Another meta-analysis found significant differences in zinc levels between individuals living

with ASD and healthy counterparts (Babaknejad et al. 2016). In addition, studies have shown significant differences in protein intake, calcium, and other factors between people with and without ASD (Sharp et al. 2013). However, as previously noted, the results of these studies are inadequate for several reasons, including inadequacy in design, inconsistency in findings, or indirect nature pinpointing mere associations rather than correlations (Modabbernia et al. 2017).

When discussing folic acid, Castro et al. (2016) conducted a systematic review to assess the involvement of vitamin B9 in ASD. The review showed that, even though some studies report lower levels of folate in individuals with ASD, the findings are overall inconsistent and dependent on self-reports. Another systematic review, however, concluded that folic acid deficiency may interact with certain polymorphisms in the methylene tetrahydrofolate reductase (MTHFR) gene to augment ASD risk (Pu et al. 2013). More studies are needed to establish the effects of folic acid deficiency on ASD, as well as the efficacy of folate-enhancing interventions in ASD prevention.

Another misinterpreted cause of autism is high sugar intake. While it is established that sugar intake in humans negatively impacts the brain, affecting executive (Cohen et al. 2016) and memory function (Reichelt et al. 2015), attributing autism solely to sugar is a distortion of a multi-faceted complex neuropsychiatric condition. ASD is comorbid with attention-deficit/hyperactivity disorder in 50–70% of cases (Rong et al. 2021). Because sugar reduction can help improve concentration and decrease impulsivity, therefore alleviating the shared symptoms, it may be used to control some facets of ASD. However, sugar is not considered a cause of the syndrome (Marti 2014).

The most common alternative nutritional therapy for autism is the gluten-free casein-free (GFCF) diet, which suggests eliminating food containing gluten and casein from a child's diet (Network 2008). Gluten is a protein found in grains like wheat, barley, and rye, while casein is a protein found in dairy. This diet was suggested under the hypothesis that individuals with ASD have difficulty metabolizing these proteins (Whiteley et al. 1999). However, the studies supporting this hypothesis have several limitations: Children's adherence to the diet was not measured, results were based on parents' reports where parents were not blinded to the intervention, and there was a moderate level of attrition bias (Knivsberg et al. 2002; Whiteley et al. 2010). A randomized controlled trial placing 13 children with ASD on the GFCF diet showed no efficacy in alleviating autism symptoms compared to children on a regular diet (Elder et al. 2006). A more elaborate and recent double-blinded challenge trial also showed that the GFCF diet does not significantly affect measures of physiologic functioning, behavior problems, or autism symptoms (Hyman et al. 2016). However, a recently published meta-analysis suggested that a GFCF diet may contribute to reducing stereotypical behaviors and improving cognition in children with ASD (Quan et al. 2022). To date, there is no identified nutritional deficiency directly associated with ASD onset. In addition, no specific diets have been effectively established to treat or control ASD symptoms.

16.3.2 Mood Disorders

The effect of dietary glycemic index on mental health is widely studied. Some research has shown that a diet characterized by a high glycemic index score (i.e., a high-carbohydrate diet) may exacerbate systemic inflammation, a mechanism known to be involved in depression (Buyken et al. 2014). Previous longitudinal studies show a plausible association between dietary glycemic index and the incidence of depressive symptoms (Gangwisch et al. 2015). Along the same lines, clinical studies have shown a large effect of refined carbohydrates on mood, such that a high glycemic load increases depressive symptoms in healthy volunteers (Salari-Moghaddam et al. 2019). Given its low glycemic index properties, the Mediterranean diet (which is rich in fresh fruits and vegetables, whole grains, fish, and virgin olive oil) has been gaining interest for its protective effects on mental health, linking it to decreased risk of depression (Liu 2023). Another systematic review that included 44 studies assessing the link between diet quality and anxiety and depression showed Mediterranean diet indices to be strongly associated with reduced symptoms of depression (Eliby et al. 2023). However, the sole use of the Mediterranean diet in the prevention and treatment of clinical depression could not prove any definite relationship between depression and the quality of diet (Firth et al. 2020).

On the treatment level, herbal supplements that target brain chemicals, serotonin, and noradrenaline have been widely prescribed for the treatment of depression. St John's Wort (*Hypericum perforatum*), for example, is a largely unregulated herbal supplement commonly prescribed as an antidepressant, reaching more than 2.7 million prescriptions every year (Hennessy et al. 2002). Historically, more data were needed to assess its use and effect on clinical depression (Gaster and Holroyd 2000; Ng et al. 2017; Shelton et al. 2001). More recently, a systematic review concluded that St John's Wort was comparable, if not more efficacious, than most standard antidepressants and had fewer adverse effects (Canenguez Benitez et al. 2022). Along the same lines, a meta-analysis of 14 randomized clinical trials supported the use of St John's Wort for depression, while having fewer side effects than typical medications. The authors recommended the use of St. John's Wort as a cost-effective and safe treatment strategy for mild-to-moderate depression (Zhao et al. 2023).

Similarly, several systematic reviews and meta-analyses have assessed the efficacy of omega-3 supplements in the prevention and management of depression and anxiety in adults (Liao et al. 2019; Schefft et al. 2017). The International Society for Nutritional Psychiatry endorses the use of omega-3 polyunsaturated fatty acids as a treatment for depression (Guu et al. 2019). The panel particularly recommends either pure eicosapentaenoic acid (EPA) or an EPA/docosahexaenoic acid (DHA) combination of a ratio higher than 2, with a daily dose of 1–2 g of net EPA daily (Guu et al. 2019).

16.3.3 Schizophrenia Spectrum and Other Psychotic Disorders

The relationship between schizophrenia and nutrition has long been studied. In a review analyzing dietary patterns in individuals with schizophrenia, Dipasquale and colleagues concluded that affected individuals have a poor diet, characterized by a high intake of saturated fat. This puts them at risk of developing metabolic abnormalities and adds to other risk factors, including antipsychotic treatment, smoking, and low physical activity (Dipasquale et al. 2013). A more recent study hypothesized that schizophrenia is associated with a high risk of obesity and diabetes, irrespective of sociodemographic characteristics and prescribed antipsychotics (Annamalai et al. 2017). To further support this claim, a systematic review and meta-analysis of the food intake of individuals with severe mental illness revealed that a cereal diet was positively associated with schizophrenia, while vegetable and fruit intake was not. It also reconfirmed that people with schizophrenia spectrum disorder have less healthy dietary patterns compared to healthy counterparts (Teasdale et al. 2019).

Following that note, a ketogenetic diet intervention, which mainly consists of reducing carbohydrate intake and increasing fat intake, was associated with a decrease in positive and negative symptoms of schizophrenia (Danan et al. 2022). Two case studies also described how, after following a ketogenic diet, patients started to exhibit improvement in psychotic symptoms and mood, reduction in suicidal thoughts, and weight loss (Palmer et al. 2019).

Omega-3 fatty acid intake was hypothesized to attenuate symptoms of schizophrenia. However, several meta-analyses found that supplementation did not affect symptoms of psychosis nor relapse prevention, although it may be beneficial for preventing the progression of the disorder, particularly in the early stages (Chen et al. 2015; Fusar-Poli and Berger 2012; Sommer et al. 2014). A more recent systematic review found equivocal evidence for omega-3 use in first-episode psychosis. However, the authors suggested that supplementation might be beneficial in certain subgroups, particularly those with negative symptoms and high oxidative stress and inflammation (Firth et al. 2018). Hsu et al. (2020) noted that supplementation is effective in young adults in the prodromal phase who have low baseline levels of polyunsaturated fatty acids (particularly docosahexaenoic acid), but more clinical trials are warranted.

On another hand, a review of schizophrenia spectrum disorders showcased that affected individuals have a disturbance of their microbiota-gut-brain axis. This axis, which connects the intestinal flora and the central nervous system, displays several alterations in this population, at the level of the immune system function, neurotransmitter synthesis, and neurotransmitter pathways. The authors also noted several vitamin and mineral deficiencies in individuals with schizophrenia, including folate, vitamin D, and vitamin C. However, besides promising evidence of methyl folate and N-acetylcysteine supplementation, there was limited evidence for the effectiveness of any other nutrient supplementation in schizophrenia, whether as a standalone or adjunctive treatment (Teasdale et al. 2020).

In conclusion, a compelling rationale exists for the role of diet in safeguarding at least physical health in psychosis. More studies are needed to establish the potential preventative or therapeutic benefits that nutritional interventions might have in schizophrenia.

16.3.4 Substance Use Disorders (SUD)

The association between SUDs, health, and nutrition has long been studied. Individuals who use substances are described as having an unhealthy lifestyle when it comes to their food intake (Mahboub et al. 2021; Saeland et al. 2011; White 2010). In a study conducted on individuals living with SUDs, more than half of the sample reported not having unlimited access to food due to lack of money. In addition, females reported choosing more unhealthy food choices (Saeland et al. 2011). Similar findings were noted in an Australian sample of participants enrolled in a methadone maintenance program, where intake of food high on energy and protein was found to be low, contrary to the intake of sugars (Zador et al. 1996). A recent narrative review about the dietary patterns of individuals living with SUDs highlighted their unhealthy food choices, especially their preference for sweet taste and intake of sugar. This is commonly observed during periods of drug misuse and early in abstinence. However, later in recovery, sugar cravings gradually wane off and transition into a more structured food intake and improved appetite (Mahboub et al. 2021). An excessive intake of glucose may play a role in brain areas and neural pathways responsible for reward, motivation, and desire for pleasure. Furthermore, a high intake of sugar may facilitate the release of dopamine, an effect observed in drug use. This resemblance between drugs and sugar intake was showcased by Witek and colleagues who explained how sugar acts as an addictive substance altering the mood, appetite, memory, and behavior and causing withdrawal, mimicking drug use (Witek et al. 2022).

Other studies also suggested that food high in carbohydrates, low in vitamins and minerals, and deficient in proteins is usually consumed among individuals living with SUDs (Himmelgreen et al. 1998; Morabia et al. 1989; Neale et al. 2012). Affected individuals also reported a preference for taking drugs over food. However, those who stop misusing substances experience a renewed enjoyment of eating, resulting in weight gain, especially during the initial stages of recovery (Neale et al. 2012).

Alternatively, the intake of certain nutrients, such as amino acids and omega-3 fatty acids, has been suggested as a potential avenue to decrease drug relapse (Mahboub et al. 2021). One randomized controlled trial of omega-3 versus placebo in males with alcohol dependence found that those in the former group had a lower number of alcohol consumption days at 2 and 3 months of discharge from the hospital, warranting further investigations (Pauluci et al. 2022).

16.4 Food Types, Lifestyles, Diets, and Mental Health

16.4.1 Red Meat and Mental Health

Data about meat consumption and mental health are unequivocal. Red meat is a rich source of proteins, vitamin B complexes, and minerals such as zinc and iron, all of which are essential for appropriate functioning of neurotransmitters. Alternatively, the different saturated fatty acids in red meat are linked to increased inflammation, which might explain the inconsistencies in the information on the relationship between red meat consumption and mental health outcomes (Mofrad et al. 2021). Carroll and Doherty (2019) and Johnston et al. (2019) suggested that the evidence supporting public health recommendations to advise reduction or elimination of meat consumption has been based on questionable research. Factors that can account for contradictory associations between meat consumption/abstention and mental health outcomes include variations in research designs and sampling methods, inconsistency between self-reported and actual intake, lack of objective tools for assessment of meat intake, and the inconsistent/intersecting definitions in self-reported meat consumption (from being "vegetarian" to avoiding both red and white meat).

One group of researchers examined the relationship between meat avoidance and mental well-being. The analysis included 18 studies encompassing a sample of 160,257 participants, which includes 149,559 meat consumers and 8584 meat abstainers, from multiple geographic regions. Studies substantially varied in methodologic rigor and confidence in results. Most studies showed that meat abstainers had significantly higher rates or risk of anxiety, depression, and self-harm behaviors compared to consumers (Dobersek et al. 2021). The same group of authors looked at the other side of the coin: meat consumption and psychological health in 22 studies (171,802 participants with 157,778 meat consumers and 13,259 meat abstainers). Along the same lines, compared to abstention, meat consumption was significantly associated with lower levels of depression and anxiety (Dobersek et al. 2023). Alternatively, one meta-analysis of 17 longitudinal studies assessed the association between red and processed meat consumption and depression. Pooled data suggested a statistically significant detrimental effect of red and processed meat intake on prevalent depression (Nucci et al. 2020). Further studies that take into consideration the above-mentioned research limitations are needed to better understand the association between red meat consumption and mental health.

16.4.2 Dairy Products and Mental Health

The relationship between dairy products and mental health is complex. Dairy products contain tryptophan, the precursor of serotonin. They also contain several important micronutrients, including calcium, vitamins B12 and D, and omega-3 fatty acids, all associated with depression and anxiety whenever deficient.

A small body of literature looked at the consumption of dairy products, mental health outcomes, and cognition. Most studies discuss the relationship through its mediation with calcium, wherein low dairy calcium has been, for instance, linked with insomnia (Alkhatatbeh et al. 2021a, b) and depression (Bae and Kim 2012). A recent cross-sectional study among 1233 college students in the United States showed that higher dairy and calcium intake was associated with less perceived stress and higher positive mood scores. Calcium intake was associated with decreased anxiety and rumination scores. Furthermore, increased calcium intake weakened the relationship between perceived stress and anxiety/negative mood. Alternatively, dairy intake did not exhibit the same effect (Du et al. 2022). Another cross-sectional study among 7387 adults in Iran showed that total milk and total yogurt consumption were significantly associated with decreased depression odds. Similarly, total milk, dairy, and kashk consumption were significantly associated with decreased anxiety symptoms. Alternatively, a higher intake of cheese was associated with greater stress odds. The authors concluded that, overall, both high- and low-fat dairy products were associated with a reduced prevalence of psychological disorders (Mahdavifar et al. 2022). One study particularly looked at whole- and low-fat dairy products and their association with self-reported cognitive function and psychological well-being among 432 men and 751 women. Consuming low-fat yogurt was associated with increased memory recall quality and better social functioning in men. Along the same lines, intake of low-fat cheese was associated with better social functioning and less stress in women. Alternatively, the consumption of whole-fat dairy products was associated with increased stress, anxiety, depression, cognitive failures, and poorer memory functioning (Crichton et al. 2010b).

When particularly assessing dairy consumption and cognitive outcomes, two systematic reviews looked at the evidence of this association. In their analysis of three cross-sectional and five prospective studies, Crichton et al. found that poorer cognitive function and a higher risk for vascular dementia were associated with lower milk or dairy product consumption in the elderly. Conversely, the intake of whole-fat products was linked with cognitive decline (Crichton et al. 2010a). A more recent systematic review of five prospective cohort studies and one randomized controlled trial had contradictory findings on the relationship between dairy intake and cognitive decline/risk of developing Alzheimer's disease (Cuesta-Triana et al. 2019).

In conclusion, due to variations in research methods and limitations in existing studies, it is currently not possible to draw definitive conclusions about the relationship between dairy consumption, cognitive performance, and mental health.

16.4.3 Tea and Mental Health

Interest in the effects of tea (*Camellia sinensis*) on mental health has recently emerged, prompting research to look into components in tea that may help treat mental disorders and cognitive decline (Lardner 2014). Historically, tea has been linked with promoting calmness, alleviating stress, and decreasing alertness. These effects are mediated by L-theanine, a type of non-protein amino acid extracted from tea leaves. As a naturally occurring structural analog of glutamate, L-theanine crosses the blood-brain barrier, binds to glutamatergic receptors, and decreases neurotoxicity, therefore helping with relaxation and improving mood and cognition (Wang et al. 2022). A recent review particularly highlights the benefits of various tea compounds, including L-theanine, in mediating the pathophysiological mechanisms of depression. This includes effects on the monoaminergic systems, the stress response mediated by the hypothalamic-pituitary-adrenal axis, inflammation, and neurogenesis (Lange et al. 2022).

In clinical research, studies on the association between tea and mental health show inconsistent results. One cross-sectional study looked at whether daily green tea consumption was associated with positive mental health outcomes among 380 adults from Japan. After adjusting for age, perceived mental stress, and intake of caffeine, green tea consumption was not associated with any noticeable decrease in the risk of mental illness (Shimbo et al. 2005). Two systematic reviews looked at caffeine and/or tea consumption and the risk of depression. One study found a borderline nonsignificant association between drinking tea and depression, suggesting a partially protective effect of tea on depression risk (Grosso et al. 2016). The second systematic review and dose-response meta-analysis of observational studies found no correlation between tea consumption and reduced depressive symptoms (Torabynasab et al. 2023). One meta-analysis only looked at studies assessing tea consumption and depression risk (22,817 participants with 4743 cases of depression). Compared to those with lower tea consumption, individuals with higher tea consumption had a pooled relative risk of depression risk at 0.69 (95% confidence interval 0.63–0.75). There was a linear association between tea consumption and the risk of depression, with an increment of 3 cups/day significantly associated with a decreased risk of 37% (relative risk of 0.63, 95% confidence interval 0.55–0.71). The meta-analysis concluded that tea consumption can attenuate depression risk (Dong et al. 2015).

In terms of anxiety, an old study found no significant association between tea consumption and symptoms of anxiety among 3854 respondents to the National Center for Health Statistics Health and Nutrition Examination Survey (Eaton and McLeod 1984). More recently, a systematic review assessed the impact of L-theanine supplementation (200–400 mg/day) on stress response and anxiety levels. Findings from 9 randomized controlled trials showed that L-theanine may assist in decreasing stress and anxiety in individuals exposed to stressful situations (Williams et al. 2020). When looking at cognition, a cross-sectional study that included 972 Chinese older adults found that, in contrast to non-tea drinkers, a decreased risk of

cognitive delay was observed in both green and other types of tea drinkers after adjusting for demographic, lifestyle, and body health variables. Furthermore, a significant association was found between tea consumption and improved cognitive performance (Yin et al. 2022).

While tea might have beneficial effects on mental health and cognition, the results of studies are either inconclusive or potentially of limited clinical effects. Further randomized controlled intervention studies are needed to establish a sturdier relationship between bioactive compounds in tea and depression, anxiety, and cognitive decline.

16.4.4 The Ketogenic Diet

The ketogenic diet is a "high-fat, low-carbohydrate" diet, in which the body generates ketones to use as a primary energy source (Rogovik and Goldman 2010). This diet is hypothesized to increase the γ-aminobutyric acid (GABA)-to-glutamate ratio in the brain and alter sodium and calcium levels, consequently alleviating positive symptoms of psychotic disorders (Włodarczyk et al. 2018) and mood disorders (Phelps et al. 2013), respectively. A literature review by Niepotter and Gopalan (2019) discusses the impact of such diet on mitochondrial function and how it subsequently impacts neuropsychiatric symptoms as per findings in preclinical studies on rats and clinical case reports. Most of the clinical evidence assessing the benefit of a ketogenic diet in schizophrenia (Kraft and Westman 2009), major depressive disorder (Cox et al. 2019), and bipolar disorder (Campbell and Campbell 2019; Phelps et al. 2013) are from either observational or case studies. A more recent retrospective analysis of 31 inpatients with refractory, severe, and persistent mental illness showed that placement on a ketogenic diet was associated with significant improvements in depressive and psychotic symptoms and was a well-tolerated and feasible approach (Danan et al. 2022). Overall, the role of the ketogenic diet in the treatment of mental health symptoms remains limited. Furthermore, the benefits and risks of such a diet should be considered for each individual before implementing any dietary change (Tillery et al. 2021). Larger studies with a high number of participants and randomized trials are crucial to establish the effect and safety of the ketogenic diet in psychiatric disorders.

16.4.5 The Gluten-Free Diet

Gluten is a mixture of water-insoluble prolamin proteins found in wheat, barley, rye, and other cereals (Wen et al. 2012). Celiac disease (CD) is an autoimmune disorder in which the ingestion of gluten induces damage to the small intestine and an array of gastrointestinal symptoms, among others (de Lourdes Moreno et al. 2017). A gluten-free diet is the mainstay treatment for CD (Aljada et al. 2021).

When it comes to mental health, research suggests potential advantages of a gluten-free diet in managing depression, although studies are scarce and require further investigation (Busby et al. 2018). Peters et al. (2014) conducted a randomized controlled trial involving 22 individuals diagnosed with irritable bowel syndrome who tested negative for CD. Participants were randomized to a diet either supplemented or not supplemented with gluten. Interestingly, depression scores were higher in the gluten group compared to the placebo. Alternatively, a large cross-sectional survey among 22,274 participants found no difference in depression scores among patients with CD, gluten avoiders, and healthy controls (Zylberberg et al. 2017). In the same study, CD antibodies, such as anti-gliadin and transglutaminase 6 antibodies, were found in patients with schizophrenia without a CD diagnosis. This suggests a plausible link between gluten and psychosis (Zylberberg et al. 2017). Looking into this question, a systematic review by Ergün et al. (2018) review showed that there were conflicting results in the various clinical, immunological, microbiological, and epidemiological studies that investigated the relationship between schizophrenia and gluten. Some studies noted improvement in schizophrenia upon gluten elimination, but all articles included were observational, except for one small trial. The role of a gluten-free diet in ASD was previously discussed. A recent review of the literature suggested considering providing a gluten and casein-free diet in individuals living with mental health who are intolerant or allergic to either element, as such intervention can potentially improve their psychiatric symptoms (Ulaş et al. 2022).

16.4.6 The Paleolithic Diet

The Paleolithic diet is based on foods believed to have been consumed by ancient hunter-gatherers, including red meat, poultry, fish, vegetables, fruits, nuts, seeds, herbs, spices, and certain oils, while excluding grains, beans, dairy, processed foods, certain oils, and added sugar (Singh and Singh 2023). To date, minimal research links the paleo diet to improvements in mental health. One cross-sectional study showed that following a Paleolithic diet was significantly associated with lower odds of depression, anxiety, and stress (Zamani et al. 2023). A randomized controlled trial of the Paleolithic versus usual diet in individuals with relapsing-remitting multiple sclerosis showed that the former diet was associated with a reduction of perceived fatigue and increased mental quality of life, among other variables (Irish et al. 2017). Alternatively, there is some evidence that following a Paleolithic diet increases the risk of developing an ED (Ambwani et al. 2019).

16.5 Clinical Recommendations and Conclusions

In this chapter, we provide a summary of evidence on the role of diet and various supplements in mental health and psychiatric disorders, while clarifying any related misconceptions on the matter. As it currently stands, the association between nutrition and mental health is mostly highlighted through epidemiological research. However, these data do not provide information about causality or underlying mechanisms. Diet modifications might have the potential to prevent and treat psychiatric symptoms. Yet, nutrition is only part of a matrix of complex elements that impact psychopathology and the response to treatment. In the realm of data, it seems that omega-3 fatty acids and St. John's wort have the most solid evidence for potential benefits in treating psychiatric symptoms. However, any provision of these supplements or other nutrients is rather, a part of a larger and intricate treatment plan that takes into consideration several factors including the individual's sociodemographic characteristics, clinical presentation and symptomatology, past trials of medications and response, medical comorbidities, current intake of medications and potentially other supplements, the safety of the considered nutrient, availability, and cost. More research is vital while taking into consideration the above factors and confounding variables. Indeed, current studies remain often methodologically limited, due to small sample sizes and lack of blinding in treatment allocation, among other factors. Studies require more robust designs that not only include large sample sizes, but also appropriately define types of diets, content of supplements, and nutritional interventions using universal standardized tools. This would allow better comparison of inter-research findings. More importantly, mental health issues change across one's lifespan and are influenced by genetics, hereditary factors, and the environment. Nutrition, diet, and lifestyle also vary across the lifespan. Therefore, any dietary recommendations to improve mental health should be personalized while considering these factors.

We conclude with a set of recommendations that can guide the use of supplements and the incorporation of nutritional psychiatry in everyday's clinical assessment:

- Always inquire about the intake of supplements, nutrients, minerals, herbs, vitamins, and other over-the-counter medications as part of your clinical assessment.
- If possible, use a standardized questionnaire to gather information about the patient's dietary habits, supplement use, and overall nutritional status. This can be incorporated into the initial assessment.
- Always consider screening for EDs as part of your initial clinical assessment.
- Collaborate with other mental health professionals and clinicians as part of a holistic multidisciplinary plan that is individualized and targeted to the needs of your patient. Tailor your treatment based on individual characteristics, including but not limited to age, lifestyle, and genetics.
- As part of your multidisciplinary team, actively involve a registered dietitian or nutritionist in the treatment plan. They are the experts when it comes to creating

personalized dietary plans while taking into consideration needs, preferences, and restrictions.
- Consider using supplements as adjuncts in treatment, especially if a deficiency is documented.
- Consider using supplements with the most evidence, but when clinically applicable.
- If supplements are prescribed, be mindful of relevant drug-drug interactions or toxicities if taken excessively.
- Explain to patients the potential risks or downsides associated with supplement use, especially when not properly monitored. Recommend avoiding self-prescribing supplements without seeking medical advice.
- Provide patients with trusted and evidence-based educational materials on nutrition and mental health. Encourage them to learn about the role of a balanced diet and how certain nutrients can positively impact their well-being.

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Part III
Nutritional Treatment of Psychiatric Disorders

Chapter 17
Psychopharmacology of Psychiatric Disorders and Food Intake

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Abstract This book chapter delves into the intricate relationship between psychopharmacology, psychiatric disorders, and food intake. Psychiatric disorders such as depression, anxiety, bipolar disorder, and schizophrenia are often associated with alterations in appetite, eating behaviors, and food preferences, which can profoundly impact nutritional status and overall health outcomes. The chapter explores the multifaceted effects of psychotropic medications on food intake, metabolism, and weight regulation, elucidating both therapeutic and adverse effects. Furthermore, it examines the bidirectional influence between nutritional factors and psychotropic medications, emphasizing the importance of a comprehensive approach to treatment that considers both pharmacological and dietary interventions. Insights from preclinical and clinical studies shed light on the complex mechanisms underlying the interplay between psychopharmacology and food intake, offering valuable implications for personalized treatment strategies and the management of psychiatric disorders.

Keywords Psychopharmacology · Psychiatric disorders · Food intake · Psychotropic medications · Mental health

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17.1 Introduction

Psychiatric disorders or mental health disorders are dysfunctions of behavior, emotions, or cognition associated with distress or impairment in social, occupational, or interpersonal functioning that is clinically significant (Elleker et al. 2014). The American Psychiatric Association (APA) publishes the Diagnostic and Statistical Manual of Mental Disorders (DSM), which is a classification and diagnostic tool for mental health disorders (Regier et al. 2013). Psychopharmacology is the study of the effects, mechanisms, and uses of psychoactive substances on the brain (Kapalka 2010). These psychoactive substances are altering people's perceptions, emotions, states of awareness, or behaviors (Miller et al. 2015). They can be used for the treatment of psychiatric disorders but on the other hand, they can induce psychological problems (Okpataku et al. 2014; Schifano et al. 2021). Food intake and psychiatric disorders have complex relationships. An increasing number of studies indicate that food intake and psychiatric disorders may be related (Sangsefidi et al. 2020a, b). Mental health conditions can influence eating habits and nutritional patterns, as well as diet and nutrition affecting mental health (Hoerr et al. 2017; Banta et al. 2019; Grajek et al. 2022).

17.2 Depression and Mood Disorders

Depression is a complex and prevalent mental health disorder that profoundly affects individuals' thoughts, emotions, behaviors, and physical health, leading to substantial disruptions in daily functioning and overall well-being (LeMoult and Gotlib 2019). Individuals experiencing depression often suffer persistent feelings of low mood, anhedonia, and cognitive changes (Schmidt et al. 2011). The prevalence of depression is estimated to be 3.8% of the global population, affecting over 280 million individuals. Additionally, over 700,000 deaths occur annually as a result of suicide, making it the fourth leading cause of death in 15- to 29-year-olds, according to the World Health Organization (Institute of Health Metrics and Evaluation 2021).

17.2.1 The Pathophysiology of Depression

Despite numerous hypotheses attempting to elucidate the molecular pathophysiology of depression, the precise underlying cause remains elusive. The monoamine hypothesis of depression, however, remains a prominent theory proposing that the primary symptoms of depression arise from a functional deficiency in brain monoaminergic transmitters, namely norepinephrine (NE), serotonin (5-HT), and/or dopamine (DA) (Hasler 2010).

17.2.1.1 Serotonin and Norepinephrine

Serotonin stands as the extensively explored neurotransmitter in depression. The strongest evidence supporting the compromised function of the central serotonergic system arises from studies centered on tryptophan depletion. This deliberate reduction in central serotonin synthesis among depressive patients correlates with the emergence of depressive symptoms, particularly in individuals at higher risk of experiencing depression (Liu, et al. 2017, Correia and Vale 2024). Additionally, it is thought that the pathophysiology of Major Depressive Disorder (MDD) involves dysfunction in the central noradrenergic system. This hypothesis is supported by evidence indicating reduced norepinephrine metabolism, higher tyrosine hydroxylase activity, and diminished density of the norepinephrine transporter within the locus coeruleus among individuals with depression (Charney and Manji 2004).

17.2.1.2 Dopamine

While historical neurobiological theories regarding depression have primarily centered on serotonin and norepinephrine, there is a growing interest in the involvement of dopamine (Nutt et al. 2006). Evidence from studies observing reduced levels of dopamine metabolites in cerebrospinal fluid and jugular vein plasma of depressed individuals suggests a potential decrease in dopamine turnover (Lambert et al. 2000). Previous studies revealed that depression is linked not only to general dietary patterns (Molendijk et al. 2018) but also to specific food and beverage consumption, including fish, coffee, fruits, and vegetables (Liu et al. 2016). Numerous prospective studies have revealed a correlation between an increased risk of depression and the consumption of unhealthy Western diets rich in sweetened beverages, processed meats, fried foods, and refined grains (Lang et al. 2015).

17.2.2 Nutritional Factors Influencing Depression and Mood Disorder Pathophysiology

17.2.2.1 Zinc

Zinc is vital for the growth and development of the human central nervous system (CNS), playing a pivotal role in neurodevelopmental processes like neurogenesis, neuronal differentiation, and the growth of white matter (Brion et al. 2021). Its involvement as a cofactor in hundreds of enzymes is crucial for various cellular functions, including DNA synthesis, cell division, and signaling pathways (Szewczyk et al. 2011). Decreased dietary intake of zinc, along with the consumption of high-phytic acid foods—known to bind and reduce zinc absorption—contributes to zinc deficiency. Additionally, insufficient zinc absorption can result from various factors, including alcohol consumption, as ethanol affects zinc transport

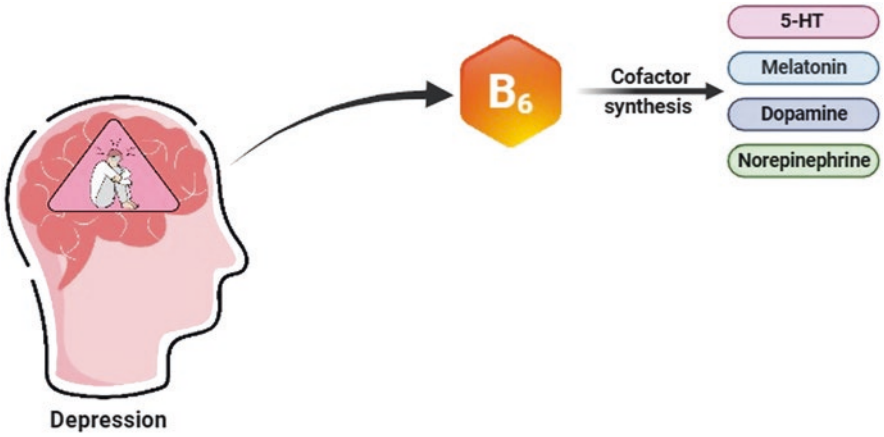

Fig. 17.1 The role of vitamin B6 in the synthesis of depression-deficient neurotransmitters

proteins, leading to lowered zinc levels in body tissues (Wang et al. 2018; Skalny et al. 2018).

17.2.2.2 Vitamin B6

Vitamin B6 is a cofactor in the brain's synthesis of key neurotransmitters like 5-HT, *N*-acetyl serotonin (Melatonin), norepinephrine, and dopamine (Fig. 17.1) (Shabbir et al. 2013). Malnutrition or deficiency in foods containing vitamin B6, such as wheat, whole-grain bread, potatoes, roast pork, and roast beef, can contribute to the onset of depression.

17.2.2.3 Iron

Iron deficiency profoundly impacts various physiological processes, including myelination, cellular functions, oxidative processes, neurotransmitter metabolism, and thyroid hormone regulation. Diminished brain iron reserves notably affect essential enzymes required for synthesizing, functioning, and degrading neurotransmitters like dopamine, serotonin, and norepinephrine (Shah et al. 2021). In women of childbearing age, iron deficiency contributes to cognitive function impairments, impacting memory, learning, and concentration. Common symptoms associated with iron deficiency encompass fatigue, irritability, apathy, and difficulties in maintaining focus. Additionally, iron deficiency, even in the absence of anemia, correlates with higher depressive scores (Ahmed et al. 2023).

17.3 Schizophrenia

Schizophrenia is a severe and chronic mental disorder that affects about 1% of the global population. It is characterized by the presence of positive symptoms such as delusions, hallucinations, and disordered thinking, followed by negative symptoms such as decreased emotional responsiveness, cognitive activity, and social motivation. This disorder often results in a substantial decline in daily function, lifelong impairment, and considerable distress. Furthermore, there is growing evidence that schizophrenia results in cognitive deficits, particularly in attention, memory, and executive functions, which significantly contribute to the disability associated with schizophrenia (Ibrahim et al. 2022; Nawwar et al. 2022).

17.3.1 Schizophrenia Pathophysiology

Unlike other neuropsychiatric disorders, schizophrenia does not exhibit a consistent singular anatomical abnormality, nor does it present any biochemical assessments that definitively confirm its clinical diagnosis. However, its etiology likely comprises a complex interplay of genetic predisposition, environmental influences, neurobiological factors, immune system responses, psychological factors, gut microbiome interactions, and disruptions in neurotransmission. Schizophrenia is a multifaceted condition involving the dysregulation of numerous pathways in its underlying physiology. Robust evidence substantiates the involvement and interplay of various neurotransmitter systems—including dopaminergic, glutamatergic, GABAergic, serotonergic, and cholinergic systems—in the disorder's pathophysiology (Deng and Dean 2013). Moreover, findings from genetic studies, post-mortem analysis, and animal research conducted in the last decade have pinpointed several susceptibility factors associated with schizophrenia. These include neuregulin 1 (Nrg1) and its receptor ErbB4, disrupted-in-schizophrenia-1 (DISK1), catechol-*O*-methyl transferase (COMT), BDNF, and Akt (Karam et al. 2010). Simultaneously, preclinical models support the hypothesis that the development of schizophrenia may be related to compromised antioxidant defense mechanisms and abnormalities in inflammatory cytokines (Schiavone and Trabace 2018).

17.3.2 The Correlation Between Diet and the Incidence of Schizophrenia

Recently, nutritional factors have been reported to be significant predictors of mental health (Onaolapo and Onaolapo 2021; Cha and Yang 2020). It is also well-established that dietary composition may have an impact on an individual's risk of developing psychosis (Joseph et al. 2017). The evidence supporting the significance

of nutrition in preserving mental health emerged from the study of disorders including pellagra, beriberi, scurvy, and phenylketonuria (which are some of the earliest known human diseases with psychiatric presentations). These diseases, documented since ancient times, are characterized by psychiatric symptoms. The development of these disorders was associated with inadequacies in nutrition and was rectified through nutritional supplements (Raju 2017). Since then, ongoing studies have consistently indicated that deficiencies in various nutrients, such as vitamins B1, B6, B9, and B12, may be associated with the emergence of psychiatric symptoms or an elevated likelihood of developing mental health conditions during adulthood (Enderami et al. 2018; Smith et al. 2018). Recent studies on diet's impact on schizophrenia reveal that individuals with this condition often exhibit poor dietary habits, marked by elevated sodium, cholesterol, and saturated fat intake alongside inadequate fiber in addition to high sugar consumption, processed food, and lower levels of omega-3 fatty acids or vitamin D in diets (Brown et al. 1999; Joseph et al. 2017; Nunes et al. 2014; Strassnig et al. 2003). These dietary patterns are implicated in potential causes of obesity, metabolic syndrome, and increased mortality rates linked to schizophrenia (Ito et al. 2015; Teasdale et al. 2016). Also, deficiencies in essential fatty acids (Lakhan and Vieira 2008; Wainwright 2002), or the presence of substances triggering autoimmune reactions, like gluten, could contribute to mental illnesses like schizophrenia (O'Neil et al. 2014; Sarris et al. 2015). Furthermore, biochemical tests have indicated elevated homocysteine levels and deficiencies in vitamins B9, B12, C, and E among newly diagnosed and long-term schizophrenia patients. Reduced brain levels of vitamin B12 have also been reported (Zhang et al. 2016). Moreover, imbalances in essential trace elements such as calcium, zinc, selenium, copper, and manganese have been observed in individuals with schizophrenia (Fig. 17.2) (Rahman et al. 2009; Schumacher et al. 2002).

17.3.3 Mechanisms Through Which Nutrition and Nutritional Factors Influence Schizophrenia Pathophysiology

17.3.3.1 Neuroinflammation

Neuroinflammation, characterized by microglial activation and the presence of infiltrating leukocytes, represents a crucial defensive response within the central nervous system (CNS). Microglia, residing in the CNS, typically engage in clearing debris or combating infections through phagocytosis. However, persistent activation of microglia can lead to neuroinflammation, marked by the release of cytokines such as tumor necrosis factor-alpha, interferon-gamma, interleukin (IL-6), IL-8, and free radicals (Mansour et al. 2021a). This phenomenon of neuroinflammation is frequently observed in psychiatric conditions like schizophrenia (Sandhu et al. 2017; Leffa et al. 2018). There is compelling evidence indicating that certain dietary elements like flavonoids and omega-3 fatty acids possess neuroprotective properties, effectively reducing neuroinflammation in various psychiatric disorders. These

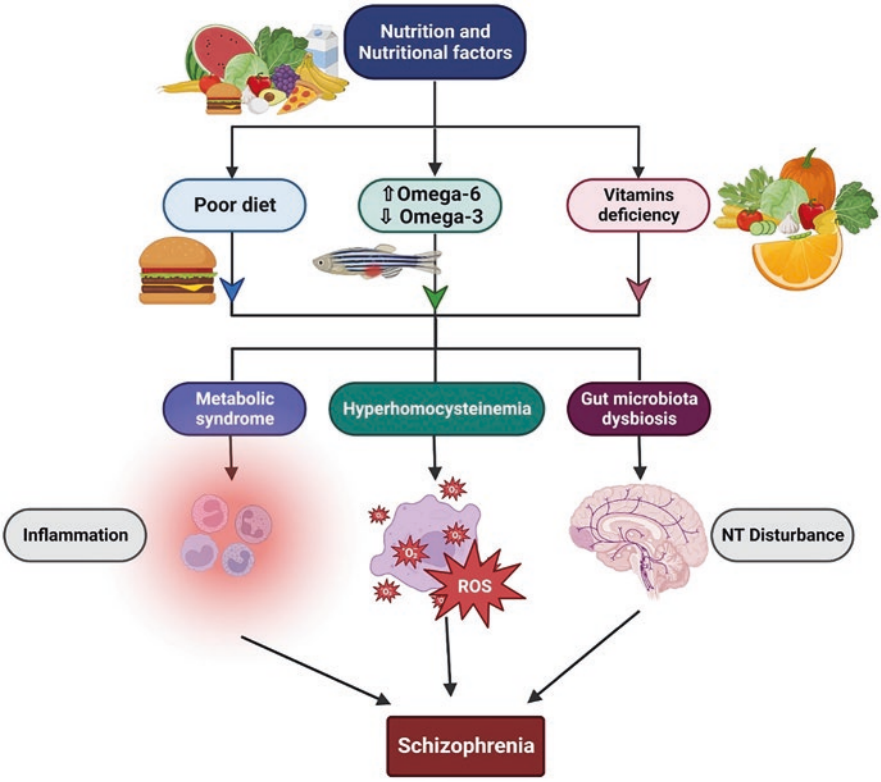

Fig. 17.2 The effect of different nutritional factors on the pathophysiology of schizophrenia

effects are linked to the suppression of cytokines, microglial activation, and the HPA axis, while also enhancing synaptic plasticity and brain-derived neurotrophic factors (Fourrier et al. 2019). Additionally, omega-3 and omega-6 fatty acids counteract neuroinflammation by competing with arachidonic acid, thereby inhibiting cyclooxygenase and lipoxygenase production (Shibata et al. 2017). Moreover, quercetin, a flavonoid found in various foods like apples, onions, nuts, tomatoes, grapes, and berries, demonstrates the ability to inhibit cytokines such as TNF-α and IL-1 produced by glial cells and macrophages. It also suppresses lipoxygenase and cyclooxygenase activity (Estrada and Contreras 2019). Additionally, vitamins exert a protective role in suppressing neuroinflammation; for instance, vitamin D may hinder the differentiation of Th17 cells while boosting the production of TGF-β (Ooi et al. 2012).

17.3.3.2 Oxidative Stress

The brain's aerobic demands necessitate a substantial supply of oxygen. However, the involvement of oxygen in psychiatric disorders arises from the generation of free radicals (Fig. 17.2) (Tardy et al. 2020). Oxidative stress is characterized by an imbalance between oxidation and antioxidant processes, leading to the excessive accumulation of oxidative molecules, including reactive nitrogen species like peroxynitrite, nitrogen oxide, and nitric oxide, as well as reactive oxygen species like hydroxyl radicals and hydrogen peroxide (Mansour et al. 2021a). Antioxidants, comprising superoxide dismutase, glutathione peroxidase, catalase, vitamin E, vitamin C, glutathione, alpha-lipoic acid, melatonin, carotenoids, zinc, copper, and selenium, counteract oxidative stress (Sies et al. 2017).

Oxidative stress significantly impacts physiological health. For instance, play essential roles in destroying pathogenic organisms, engaging in detoxification and enzymatic processes, and synthesizing physiologically useful compounds. Nevertheless, oxidative stress can also be detrimental, causing damage to cell membranes, protein denaturation, neuronal loss, and nucleic acid mutations (Mansour et al. 2021b). The central nervous system (CNS) is particularly vulnerable to oxidative stress due to various factors, including its high energy demands, presence of unsaturated fatty acids in cell membranes, excitotoxic properties of certain neurotransmitters, iron metabolism, limited antioxidant mechanisms, reactive oxygen species generated by activated microglia, and the non-replicating nature of neurons (Mansour et al. 2021c). In schizophrenia, there is an association with impaired antioxidant mechanisms, indicated by elevated levels of malondialdehyde, along with reduced levels of vitamin E and vitamin C (Maes et al. 2000; Uddin et al. 2021). Notably, magnesium deficiency contributes to oxidative stress (Mazur et al. 2007), and magnesium deficiency can hinder the antioxidant defense system as it is crucial for gamma-glutamyl transpeptidase production, essential for synthesizing glutathione (Tohidi et al. 2011). Moreover, the levels of magnesium are inversely linked to markers of oxidative stress such as malondialdehyde and superoxide anion (Barbagallo et al. 2021).

17.3.3.3 Dopamine Pathway

Dopamine plays a crucial role in regulating emotional learning, perception, and memory formation. Dysregulated activity in dopaminergic neurons is linked to the emergence of schizophrenia symptoms (Berke 2018). In schizophrenia, there is an observed increase in dopamine release, leading to an imbalance between excessive subcortical dopamine release and deficient cortical dopamine, a significant factor in the disorder's development (Weinstein et al. 2017). Excessive activation of dopaminergic neurons contributes to positive symptoms like hallucinations, while negative symptoms are associated with reduced dopaminergic activity in the mesocortical area extending to the ventromedial prefrontal cortex. The dysregulation of dopamine is strongly linked to schizophrenia symptoms (Karakuş et al. 2017). Tyrosine,

an essential amino acid, easily crosses the blood-brain barrier and serves as a precursor for dopamine in the brain. The brain's dopamine concentration relies on the availability of dietary tyrosine, which is rapidly metabolized and requires cofactors like folic acid, copper, and vitamin C. Deficiency in activating the tyrosine hydroxylase enzyme can lead to neuronal loss, affecting the dopaminergic pathway and reducing tyrosine synthesis, exacerbating psychotic episodes. Tyrosine-rich foods impact tyrosine intake and subsequently dopamine release (Hensel et al. 2019; Jongkees et al. 2015). Furthermore, impaired dopaminergic transmission due to tyrosine deficiency can impair cognitive function, potentially contributing to cognitive dysfunction in individuals with schizophrenia (Wiesel et al. 2005).

17.3.3.4 Serotonin Pathway

Serotonin, a neurotransmitter predominantly found in organs like the brain, plays a crucial role in maintaining homeostatic balance. It is synthesized from tryptophan amino acid via hydroxylase enzyme using cofactors like tetrahydrobiopterin, iron, and vitamin D (Azmitia 2020). To produce serotonin in the brain, tryptophan must pass through the blood-brain barrier, a process influenced by the tryptophan and branched-chain amino acid ratio. Conditions that decrease branched-chain amino acids, like exercise, can increase tryptophan passage into the brain (Do et al. 2010; Patrick and Ames 2015). Serotonin disturbance in the brain potentially contributes to the negative symptoms and elevated depression rates observed in individuals with schizophrenia. Evidence supporting this theory includes the effectiveness of selective serotonin reuptake inhibitors in treating these negative symptoms. Additionally, experiments involving acute tryptophan depletion, which decreases brain serotonin synthesis, have demonstrated a worsening of negative symptoms in individuals with schizophrenia (Eggers 2013). Adequate levels of EPA are essential for the release of 5-hydroxytryptophan from presynaptic neurons, while sufficient DHA levels are necessary for receptor binding in postsynaptic neurons. Insufficient EPA, DHA, and vitamin D levels can disrupt the serotonin synthesis pathway, leading to abnormal serotonin levels and behavioral issues (Patrick and Ames 2015).

17.3.3.5 Glutamate Pathway

Glutamate, is a non-essential amino acid and the most abundant excitatory neurotransmitter released by nerve cells in your brain. It plays a dual role in neurotransmission by activating dopamine release while inhibiting GABA release. The neurotransmitter glutamate, particularly its interaction with the *N*-methyl-D-aspartate receptor (NMDA-R), holds a crucial position in fundamental brain functions like neural plasticity, network formation, and CNS repair. However, excessive glutamate levels are linked to excitotoxicity and neural degeneration (Kruse and Bustillo 2022). The antagonism of the NMDA-R by substances like phencyclidine (PCP) and ketamine has replicated positive symptoms of schizophrenia, aligning

with observed neurodegenerative changes. Studies have highlighted the efficacy of l-theanine, abundantly present in green tea, in stabilizing the concentration of glutaminergic neurotransmitters (Kimura et al. 2007).

17.3.3.6 Homocysteine

Elevated levels of homocysteine, a compound associated with increased oxidative stress levels, are often observed in individuals with schizophrenia. It can convert into glutathione, a crucial component of the antioxidant defense system, in the presence of pyridoxal-5-phosphates (Fig. 17.2). Vitamin B2 plays a role in forming pyridoxal-5-phosphate from pyridoxine, indirectly affecting this pathway, while vitamin B6 is directly involved. Studies have identified impaired glutathione function in schizophrenia, suggesting potential deficits and abnormalities in the glutathione redox cycle in affected individuals (Tsugawa et al. 2019). Another route of homocysteine metabolism leads to methionine formation, where vitamin B12 serves as a cofactor, and folic acid acts as a methyl donor. Additionally, homocysteine can convert into cysteine, and vitamin B6 plays a role in this conversion process (Burghardt and Ellingrod 2013; Kałużna-Czaplińska et al. 2013). Research has shown that deficiencies in vitamins B2, B6, B12, and folic acid lead to increased homocysteine levels, subsequently heightening oxidative stress. This scenario results in escalated DNA damage and potentially exacerbates psychotic episodes in individuals with schizophrenia (Stanger et al. 2009).

17.3.3.7 Microbiota-Gut-Brain Axis

The gut-brain axis is pivotal in understanding the interplay between dietary-related inflammation and schizophrenia. Changes in the composition of gut microbiota and their byproducts impact gut health and immune responses. Studies have noted gut dysbiosis in individuals with schizophrenia, highlighting specific bacterial genera like Succinivibrio and Corynebacterium, significantly associated with the severity of schizophrenia symptoms (Li et al. 2020). This dysbiosis could influence vulnerability to infection and inflammation, potentially accelerating the onset of schizophrenia and worsening symptom severity (Fig. 17.2). It is hypothesized that dietary elements relevant to schizophrenia exert their effects, at least in part, through the gut-brain axis. However, direct evidence linking dietary-induced inflammation and schizophrenia within the context of the gut-brain axis remains limited.

17.4 Alzheimer's Disease

Dementia is a progressive loss of mental abilities that interferes with daily life (Arvanitakis et al. 2019). Alzheimer's disease (AD) is the most common sort of dementia, impacting about 50 million people globally (Zhao and Huai 2023). As life expectancy continues to rise, more individuals are encountering age-related illnesses, among them Alzheimer's disease (AD). Presently, AD stands as the foremost cause of dementia across North America and Europe, impacting approximately 4 million individuals solely in the United States (Villars et al. 2010). Alzheimer's disease (AD) has been acknowledged as a chronic neurodegenerative ailment chiefly characterized by changes in behavior and personality, impaired memory, and a loss of cognitive ability (Haller et al. 2023). During the early 1900s, the introduction of Bielchowsky silver staining enabled the identification of neurofibrillary tangles (NFTs) and senile plaques (SPs) by Alois Alzheimer in a woman experiencing presenile dementia (McKhann et al. 1984). After that, during the early 1990s, the Consortium to Establish a Registry for AD (CERAD) introduced a neuritic plaque score that relied on the density of senile plaques (SPs) per square millimeter and the person's age. This score aimed to predict dementia, differentiating between typical brain aging and AD (Mirra et al. 1991). In the same time frame, β-amyloid was determined to be the primary constituent of SPs and β-amyloid cerebral angiopathy (Aβ-CAA) (Glenner and Wong 2012). After that, the main component of NFTs was recognized as an abnormal tau protein (Wood et al. 1986). Together with increased oxidative stress, heightened homocysteine levels, and issues in both mitochondrial and vascular functions, these alterations are believed to result in membrane breakdown and a decline in synaptic connections (DeKosky and Scheff 1990).

Presently, there is not an efficient treatment for AD, possibly due in part to the absence of a distinct underlying mechanism. Given that AD showcases the emergence of extracellular amyloid-beta (Aβ) plaques, intracellular neurofibrillary tangles, gliosis, synaptic loss, and inflammation, several theories have been proposed to elucidate AD (Petrella et al. 2019; Itagaki et al. 1989; Iqbal and Grundke-Iqbal 2002). However, the current prevention strategies of AD effectively hinge not only just on lowering amyloid levels but also on addressing a range of other biological and cognitive risk factors in a comprehensive manner (Arvanitakis et al. 2019).

There is a growing interest in the role of nutrition in the prevention or treatment of AD (Volicer 2009). For quite time, it has been established those cognitive abilities can be impacted by dietary factors. Studies indicate that a higher body mass index in middle age is linked to a heightened risk of dementia later in life. Conversely, research has demonstrated that moderate calorie restriction can potentially slow down the age-related degeneration of the cortical region in the brain (Scarmeas et al. 2006). However, numerous research I have demonstrated inconclusive findings and propose that nutritional interventions are not universally effective but rather require customization for individual patients (Middleton and Yaffe 2009).

17.4.1 Role of Dyslipidemia in Alzheimer Disease

There was a rapid growth in interest regarding lipids and how cholesterol metabolism relates to AD. Although the role of cholesterol in AD pathogenesis is controversial, dyslipidemia is an important independent risk factor for AD (Schelke et al. 2016). In animal studies, it has been observed that dietary cholesterol speeds up the accumulation of Aβ in the brain, while medications that lower cholesterol levels have the opposite effect by reducing it (Refolo et al. 2001, 2000). However, other in vitro research has demonstrated that soluble amyloid precursor protein synthesis is decreased in an environment with elevated cholesterol (Simons et al. 1998; Kojro et al. 2001), as the increased membrane level is protective by increasing the generation of plasmin, an Aβ-degrading enzyme. Moreover, it was suggested that increased cholesterol level may contribute to the production of NFTs (Zou et al. 2003). Lastly, research has demonstrated that elevated levels of oxysterols, which are oxidized cholesterol derivatives, can cause neuronal death and exocytosis (Trousson et al. 2009; Ma et al. 2010). The neuroinflammation brought on by brain damage results in an increase in the concentration of cholesterol oxidation products, and they also worsen excitotoxicity by increasing exocytosis and neurotransmitter release (Ma et al. 2010). In line, elevated levels of the cholesterol by product 24-hydroxycholesterol (24S-OHC) in both blood plasma and cerebrospinal fluid (CSF), which is specifically produced in neurons, have been associated with the initial stages of Alzheimer's disease development (van Dijkman et al. 2018). On the other hand, research studies confirmed that statins could slow the deterioration of neuropsychiatric status and significantly improve activities of daily living ability in AD patients (Fig. 17.3) (Xuan et al. 2020; Liu et al. 2022; Daneschvar et al. 2015).

17.4.2 Role of Insulin Resistance in Alzheimer Disease

Alzheimer's disease (AD), type 2 diabetes (T2D), and obesity rank among the most financially burdensome and debilitating disorders globally. The connection between cognitive decline and metabolic conditions went unnoticed for a considerable period. However, growing epidemiological data increasingly reinforces a significant link among these ailments (Crane et al. 2013; Baker et al. 2011). Indeed, the Mediterranean diet, rich in fruits, vegetables, whole grains, lean proteins (such as fish), and healthy fats (like olive oil), has shown promise in improving various health markers, including reducing insulin resistance (Fig. 17.3) (Schelke et al. 2016). It emphasizes balanced, nutrient-dense foods have been associated with several health benefits due to its anti-inflammatory and antioxidant properties. Adopting this dietary pattern can be beneficial, especially for individuals with unhealthy dietary habits or those seeking to improve their insulin sensitivity and overall health (Morris et al. 2015). On the other hand, if the patients are already maintaining a nutritious diet, incorporating specific elements into their meals, they show potential

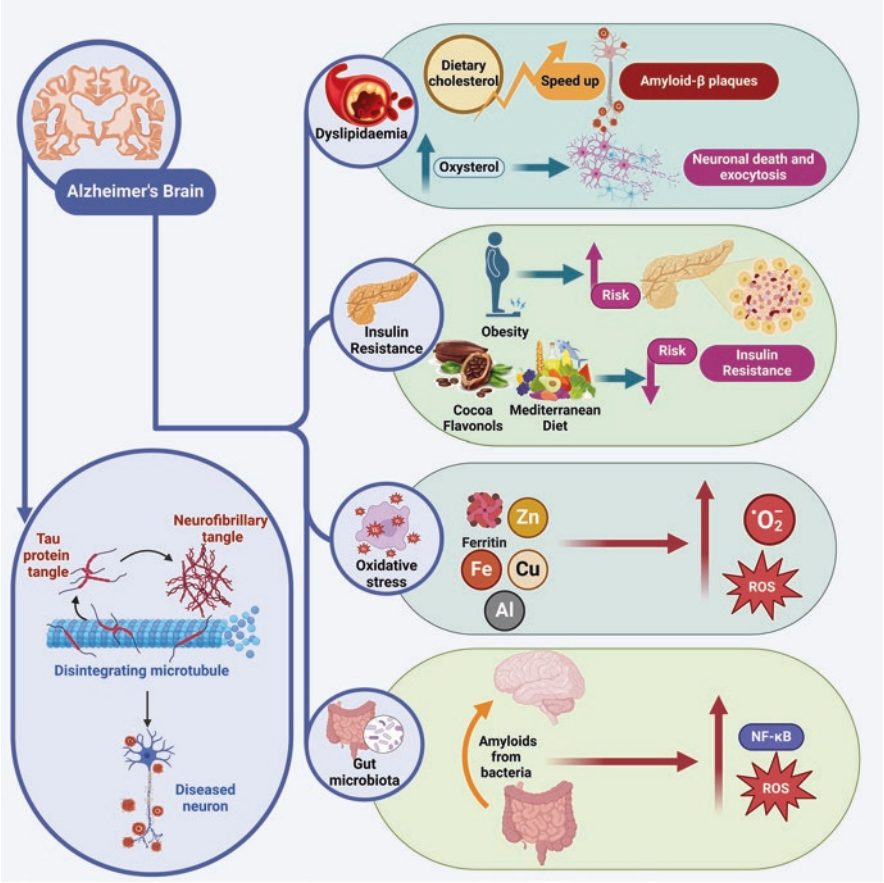

Fig. 17.3 The effect of different nutritional factors on Alzheimer's disease

in lowering the risk of Alzheimer's disease (AD). Specifically, consuming cocoa flavanols has been proven to decrease insulin resistance and enhance cognitive function in older individuals. This suggests that including cocoa flavanols in the diet could serve as a promising preventive measure against Alzheimer's disease (Mastroiacovo et al. 2015). Moreover, as obesity is linked to insulin resistance, physical exercise holds the potential for multiple benefits that could aid in reducing the risk and slowing the progression of Alzheimer's disease through various pathways. While existing evidence suggests its positive impact, more extensive human studies are required to solidify and better understand these connections (Valenzuela et al. 2020; Silva et al. 2019; De la Rosa et al. 2020).

17.4.3 Role of Oxidative Stress in Alzheimer Disease

Patients with Alzheimer's disease display notable oxidative damage in their brains, linked to the abnormal buildup of Aβ and the formation of NFTs (Christen 2000). Oxidative stress is a bridge that connects the different hypotheses and mechanisms of AD (Bai et al. 2022). The probability of this connection is reinforced by neurons' high susceptibility to damage from harmful free radicals (Tönnies and Trushina 2017). Indeed, different forms of oxidative damage have been observed in AD, such as glycation, protein oxidation, lipid peroxidation, and nucleic acid oxidation (Kozlowski et al. 2009). Additionally, Alzheimer's patients' brains show specific lesions typically linked to free radical assaults—such as DNA damage, protein oxidation, lipid peroxidation, and the presence of advanced glycosylation end products (Ionescu-Tucker and Cotman 2021). Moreover, there are metals present in these brains, like iron, copper, zinc, and aluminum, which possess catalytic properties, leading to the generation of free radicals (Plascencia-Villa and Perry 2021). Particularly, when copper (Cu) excessively accumulates within cells, it turns toxic and can trigger the production of reactive oxygen species (ROS) as well as apoptotic processes. However, it is important to note that copper is an essential trace element vital for all living organisms. It serves as the active center in enzymes like cytochrome c oxidase and other Cu-containing enzymes (Fig. 17.3) (Kamat et al. 2016). Over time, there is a gradual accumulation of iron in the brain, accompanied by rising levels of ferritin (Bai et al. 2022). This disruption in the regulation of iron and its accumulation could potentially play a role in the onset and advancement of neurodegenerative conditions like AD. In individuals with Alzheimer's disease, the brain shows distinctive characteristics, including iron buildup within senile plaques (around 1 mM) and neurofibrillary tangles. Additionally, there is a decrease in the expression of transferrin receptor in these cases (Kozlowski et al. 2009).

It is worth noting that several cross-sectional studies have examined the connection between dietary intake of antioxidants and the prevalence of Alzheimer's disease (AD). In a significant study involving individuals from 23 developed countries, it was observed that higher dietary intake of flavonoids, calculated using comprehensive dietary questionnaires, was linked to lower rates of dementia (Beking and Vieira 2010). Therefore, antioxidants found in our diets, like vitamin E, vitamin C, carotenoids, flavonoids, and phenolic acids, show potential as effective tools for preventing and treating Alzheimer's disease. These compounds are commonly present in foods we regularly eat. For instance, fruits and vegetables offer rich sources of antioxidants like vitamin C and carotenoids. Vitamin E is abundant in vegetable oils and nuts, while polyphenols can be found in tea, beer, wine, chocolate, olive oil, and berries (Otaegui-Arrazola et al. 2014).

17.4.4 Role of Gut Microbiota in Alzheimer Disease

The gut microbiota has a crucial role in influencing the two-way communication system of the gut-brain axis (Petra et al. 2015). Imbalances and changes in the composition of the gut microbiome, known as dysbiosis, have been demonstrated to be involved in the onset of various human diseases. These conditions include inflammatory bowel disease, type 2 diabetes, metabolic syndrome, obesity, allergies, colorectal cancer, and AD (Burokas et al. 2015). Specifically, changes in the gut microbiome can trigger the activation of proinflammatory cytokines and raise the permeability of the intestine. This can result in the onset of insulin resistance, which has also been linked to Alzheimer's disease (Fig. 17.3) (Bekkering et al. 2013). Moreover, the bacteria residing in the gut microbiome are recognized for releasing immune-stimulating combinations of amyloids (Mäger et al. 2014).

To illustrate the potential role of gut microbiota in Alzheimer's disease development, there is a hypothesis suggesting that amyloids produced by bacteria might escape from the gastrointestinal tract, accumulating in both the body and the brain (Zhao and Lukiw 2015). This accumulation could trigger an increase in reactive oxygen species and activate nuclear factor-κB (NF-κB) signaling (Hill and Lukiw 2015). Consequently, this signaling pathway could elevate the levels of the proinflammatory microRNA-34a (miRNA-34a). As a result, miRNA-34a might decrease the expression of TREM2 (triggering receptor expressed in microglial/myeloid cells-2), which could hinder the process of phagocytosis. This impairment in phagocytosis could contribute to the upregulation of the Aβ 42 peptide (Zhao and Lukiw 2013). However, dietary choices play a crucial role in shaping the makeup of the gut microbiota (Muegge et al. 2011). Diets that emphasize high consumption of fruits, vegetables (like rural, Mediterranean, plant-focused, or plant-based diets), and minimal meat intake are linked to a higher presence of Prevotella bacteria compared to Bacteroides organisms (Greiner et al. 2014). Prevotella bacteria are recognized for expressing genes that regulate cellulose and xylan breakdown, while Bacteroides bacteria are equipped with genes that aid in amino acid digestion (De Filippo et al. 2010).

17.4.5 Role of the Different Supplements and Food Diets in Alzheimer Disease

17.4.5.1 Omega-3 Fatty Acids

Omega-3 (n-3) polyunsaturated fatty acids (PUFAs) play a crucial role in supporting proper brain and neuronal function. These PUFAs are integral components of cell membranes and regulate vital processes like inflammation and oxidative stress (Yehuda et al. 2005). The primary n-3 PUFAs, including docosahexaenoic acid (DHA, 22:6n-3) and eicosapentaenoic acid (EPA, 20:5n-3), are pivotal for these

functions (Otaegui-Arrazola et al. 2014). Indeed, a research study demonstrated that increased plasma EPA levels were linked to reduced gray matter atrophy in the right amygdala among the general population, whereas no such association was found with DHA (Samieri et al. 2012). Moreover, high levels of plasma phosphatidylcholine DHA were significantly correlated with a 39% decreased risk of developing Alzheimer's disease in a longitudinal population-based study (Schaefer et al. 2006).

17.4.5.2 Nutraceutical Formulation

Various combined formulations, including n-3 PUFAs, antioxidants, and B vitamins, have been utilized in attempts to address Alzheimer's disease or enhance cognitive function during aging. One such recent development is Souvenaid®, a preparation comprising n-3 PUFAs (1200 mg of DHA, 300 mg of EPA), antioxidants (40 mg of vitamin E, 80 mg of vitamin C, 0.06 mg of selenium), B vitamins (0.4 mg of folic acid, 0.003 mg of vitamin B12, 1 mg of vitamin B6), along with other components like phospholipids (106 mg), choline (400 mg), and uridine monophosphate (625 mg). Clinical trials employing randomized controlled methodologies have tested Souvenaid® in individuals diagnosed with AD (Scheltens et al. 2012).

17.4.5.3 Mediterranean Diet

The Mediterranean diet is a dietary pattern inspired by the traditional eating habits of countries bordering the Mediterranean Sea, such as Greece, Italy, Spain, and southern France. It is characterized by a high consumption of fruits, vegetables, legumes, nuts, whole grains, and olive oil as the primary source of fat. Moderate intake of fish, poultry, and dairy products, particularly cheese and yogurt, is typical, while red meat is consumed sparingly. Fresh fruits as desserts and a moderate intake of red wine with meals (in some variations) are also part of this dietary pattern (Davis et al. 2015). Indeed, the Mediterranean diet has shown promise as a preventive approach within early intervention programs. Studies have indicated that adherence to this diet can enhance cognitive functions (Psaltopoulou et al. 2008), reduce the likelihood of developing disabilities, and promote better mental and physical health among healthy older individuals (Muñoz et al. 2009; Féart et al. 2011).

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Chapter 18
Supplements Effective in the Treatment of Mental Health Conditions

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Abstract The intricate relationship between nutrition and psychiatric disorders has gained widespread attention in recent years, leading to the emergence of the field of nutritional psychiatry to enhance the treatment of individuals with mental health conditions. While recognizing the modifiable impact of diet on the brain, several methodological limitations persist in evaluating dietary interventions for the prevention and treatment of psychiatric disorders. This chapter focuses on the most extensively studied supplements, citing the strongest available evidence for their role and efficacy in managing psychiatric symptoms, disorders, or related conditions. The chapter provides a comprehensive summary grounded in the latest recommendations and substantiated evidence in the field. Discussed supplements encompass melatonin, omega-3 polyunsaturated fatty acids, vitamins, minerals, amino acids, probiotics, and other selected nutrients.

Keywords Supplement · Intervention · Mental health · Psychiatric disorder · Nutritional psychiatry

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18.1 Introduction

Over the past two decades, the impact of diet and nutrition on psychiatric disorders has been increasingly acknowledged (Sarris et al. 2015a, b). The relationship between nutrition, physical health, and mental health is intricate and multidirectional (Firth et al. 2020), and there has been expanding awareness of how diet can be a modifiable risk factor influencing brain health, either preventing or treating mental illnesses (Firth et al. 2020). Ample research has been conducted to examine how dietary interventions can be incorporated into the treatment plan of psychiatric disorders, although most studies are limited methodologically, whether in terms of small sample sizes, heterogeneity in participants and supplements received, and lack of blinding, among others (Adan et al. 2019). Despite these limitations, the available evidence hints toward the importance of personalized nutrition and the consideration of dietary interventions while approaching individuals with mental illnesses.

This chapter highlights the role of supplements known to be effective in the management of psychiatric symptoms, disorders, or related medical complications. The chapter aims to be a comprehensive summary of those minerals and nutrients with the highest level of evidence in the field of nutritional psychiatry and/or commonly used in guidelines and practice. Discussed supplements include melatonin, omega-3 fatty acids, different types of vitamins, minerals, amino acids, probiotics, and other selected nutrients.

18.2 Melatonin

Although not obtained from diet, melatonin, or *N*-acetyl-5-methoxytryptamine, is one of the most commonly used over-the-counter supplements. Melatonin is a hormone produced in the pineal gland of the brain and is responsible for modulating the circadian rhythm and sleep patterns. The pineal gland releases melatonin after sundown, mostly between 11 p.m. and 3 a.m., triggering the sense of sleep. When supplemented, exogenous melatonin has this same chrono-biotic activity (Arendt and Aulinas 2022). Due to its vital role in regulating the circadian rhythm, melatonin has become a common supplement used to improve sleep and treat sleep-related conditions and disorders. Both short- and long-term use of melatonin was found to be safe and not associated with serious adverse events (Andersen et al. 2016).

Despite it not being approved by the Food and Drug Administration (FDA), the American Academy of Family Physicians considers melatonin as the first-line medication for the treatment of insomnia. It is also prescribed for the management of jet lag, shift work sleep disorder, delayed sleep phase disorder, and circadian rhythm sleep disorder (Arendt and Aulinas 2022). The French Institute of Medical Research on Sleep (SFRMS) conducted a consensus meeting to delineate other indications for the prescription of melatonin. The results, presented at the Congress on Sleep in

November 2017, highlighted the usefulness of melatonin supplementation in individuals with a psychiatric disorder who are in remission, mainly to prevent relapse in case of associated complaints of insomnia or poor sleep quality. Alternatively, in acute phases of the illness, melatonin could be used as an adjuvant treatment when insomnia symptoms are prevalent, whether in mood, anxiety, psychotic disorders, or others (Geoffroy et al. 2019).

In sleep disorders, melatonin is established to be effective in improving multiple sleep parameters such as sleep quality, efficiency, and onset latency (Moon et al. 2022). One meta-analysis suggested that both appropriate dosage and dosing time are vital to maximize the efficacy of the supplement in jet lag (Herxheimer and Petrie 2002). In particular, if melatonin is provided to manage the effects of eastward-travel jet lag, a dose of 0.1–0.3 mg at the local bedtime after the flight is advised. This will restore the deficit in melatonin that the traveler will experience due to the advance of bedtime at the destination. In opposition, after a westward flight when the day is prolonged rather than shortened, melatonin intake is not recommended as the endogenous level is already elevated. It can still be helpful to take a low dose of 0.1 mg following a night or early morning awakening to facilitate the resumption of sleep and its maintenance (Herxheimer and Petrie 2002).

Recent research highlighted the role of melatonin in depression (Tonon et al. 2021). Melatonin synthesis and secretion are primarily regulated by norepinephrine; the secretion of the former is an index of norepinephrine activity in patients with depression (Huang et al. 2015). Clinically, one study a decade ago suggested that individuals with depression might have higher levels of melatonin (Varma et al. 2002). A novel review highlighted how the central nervous system of people with depression often secretes more melatonin in the evening (Tonon et al. 2021). As melatonin prepares the body for sleep, it makes the individual feel more fatigued. As fatigue can be a core symptom of depression, if one experiences low energy during their depressive episode, taking melatonin might make their symptoms worse. When supplemented in depression, in comparison to placebo, a systematic review of eight clinical trials found that melatonin did not significantly improve symptoms (De Crescenzo et al. 2017). Similarly, a more recent meta-analysis of 19 studies (1178 participants) did not find a significant benefit from melatonin supplementation (2–25 mg/day used from 10 days to 3.5 years) in alleviating depressive symptomatology (Li et al. 2022b). Melatonin was suggested to be mostly beneficial in seasonal affective disorder, which involves depression that follows a seasonal pattern (Lewy et al. 2006).

When looking at anxiety, preclinical studies showed that melatonin can alleviate symptoms of anxiety in rats (Aziriova et al. 2014; Bustamante-García et al. 2014). This has spiked interest in the potential role of melatonin as an adjuvant to enhancing the effect of anti-anxiety medications. Melatonin's benefit in reducing anxiety may stem from multiple mechanisms of action: sympatholytic activity, antioxidant properties, modulation of inter-neuronal signaling, and impact on the glucocorticoid system (Repova et al. 2022). Clinically, this role has been particularly assessed in the preoperative setting. A qualitative systematic review found that, in 9 out of 10 trials, melatonin significantly reduced anxiety preoperatively in comparison to

placebo (Yousaf et al. 2010). Along the same lines, a recent meta-analysis of 24 trials (1794 participants) concluded that melatonin significantly decreased preoperative anxiety scores compared to placebo, although the trials were highly heterogeneous (Andersen et al. 2014).

Using melatonin in the management of schizophrenia can be traced back to the 1920s when the extraction of the pineal gland was conducted in an attempt to treat "dementia praecox" (Herrn and Friedland 2012). Later in 1961, McIsaac associated melatonin with schizophrenia when he highlighted that melatonin has a structure similar to the hallucinogenic substances harmine and harmaline and that schizophrenia typically manifests with core symptoms of hallucinations and delusions (Morera-Fumero and Abreu-Gonzalez 2013). Nowadays, melatonin is used for the treatment of comorbid sleep disorders in patients with schizophrenia. Two randomized controlled trials (RCTs) found that, compared to placebo, melatonin supplementation in individuals with chronic schizophrenia improved sleep efficiency (Shamir et al. 2000), and increased sleep duration and decreased nighttime awakenings (Kumar et al. 2007). Recently, a systematic review by Duan and colleagues found positive outcomes from the use of melatonin for sleep in individuals with schizophrenia, as well as improvements in metabolic profile and tardive dyskinesia (Duan et al. 2021).

In other conditions, melatonin was found to improve sleep quality in individuals with autism and attention-deficit hyperactivity disorder (Rzepka-Migut and Paprocka 2020; Nogueira et al. 2023). Lastly, thinking outside the box, researchers examined the association between melatonin intake and self-harm. In a cohort of 25,575 adolescents who started melatonin between ages 6 and 18, a decrease in the risk of intentional self-harm was noted following melatonin initiation. This was mostly evident in female participants with depression and anxiety (Leone et al. 2023). The findings highlighted that sleep management via melatonin could decrease the potential for self-harm in this group.

In conclusion, most of the clinical use of melatonin relates to its rhythm-resynchronizing and hypnotic properties. Emerging evidence highlights other potential roles of melatonin but more high-quality RCTs are required in that regard.

18.3 Omega-3 Fatty Acids

Interest in omega-3 polyunsaturated fatty acids (PUFAs) recently emerged in light of their multiple physical, neurologic, and mental health benefits. Omega-3 PUFAs include alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). The best food sources of PUFAs encompass specific types of fish, including salmon, sardine, and tuna, plant oils, green leafy foods, and soybeans (Shahidi and Ambigaipalan 2018).

Most of the studies on omega-3 and mental health conditions tackle schizophrenia, depression, and dementia. Omega-3 PUFAs were found to provide therapeutic benefits in 5 out of 6 RCTs in schizophrenia and 4 out of 6 trials for depression. This

advantage was mostly evident when PUFAs were added to preexisting psychotropic medications (Peet and Stokes 2005). In psychosis, preliminary studies show that adding PUFAs to the diet may help decrease symptoms. A Cochrane review of RCTs that employed omega 3 or omega 6, compared to placebo, as a stand-alone treatment or in conjunction with antipsychotic drugs included 8 trials of 517 individuals with schizophrenia or schizoaffective disorder. In most trials, EPA and DHA were compared with a placebo in individuals who were receiving stable antipsychotic treatment. A small, but statistically insignificant improvement in mental health and overall functioning was seen in a few of the studies. A study that contrasted EPA with DHA revealed a possible benefit for the former over the latter, however, the difference was also not statistically significant. Most trials were brief and modest while half were funded by the company providing the trial drug (Irving et al. 2006).

Researchers also attempted to investigate the role of fatty acids in preventing the progression to psychosis in high-risk individuals. In that regard, the meta-analysis of Deas et al. highlighted positive findings based on only two RCTs (Deas et al. 2016). Two meta-analyses found no significant impact of omega-3 PUFAs in chronic schizophrenia, although benefits might be achieved in the early stages of the disorder (Chen et al. 2015; Fusar-Poli and Berger 2012). A more recent systematic review highlighted the mixed findings about omega-3 PUFA supplementation in first-episode psychosis and noted that the impact might be highest in individuals with increased levels of inflammation and oxidative stress (Firth et al. 2018). A comprehensive literature review concluded that supplementation could be effective in individuals in the prodromal phase of the illness, particularly if they have low levels of PUFAs, mainly DHA (Hsu et al. 2020).

In depression, an exploratory meta-analysis of 35 RCTs (6665 participants who received omega-3 PUFAs and 4373 who received a placebo) found that among individuals with a diagnosis of depression, formulations that were predominately EPA (>50%) showed significant clinical benefits when compared to placebo, while DHA-predominant supplements (>50%) did not differ from placebo. Among populations without a diagnosis of depression, EPA was unable to prevent depressive symptoms (Hallahan et al. 2016). Similarly, a meta-analysis of RCTs investigating the effectiveness of PUFAs, particularly DHA and EPA, in ameliorating symptoms of depression showed that omega-3 had a significantly positive overall impact on depressive symptoms. While DHA-pure and DHA-major formulations did not show any clinical benefits when compared to placebo, EPA-pure (100% EPA) and EPA-major formulations (≥60% EPA) had significant benefits when supplemented at a dose of ≤1 g/day (Liao et al. 2019). Another Cochrane review of 35 studies examined the effects of omega-3 PUFAs in depression compared to placebo (34 studies; 1924 participants) and antidepressant treatment (1 study; 40 participants) (Appleton et al. 2021). Compared to placebo, omega-3 supplementation showed a small-to-modest, nonclinically positive effect on depression symptomology. Compared to antidepressants, the only trial of 40 participants demonstrated no differences in rates of response to treatment between groups. The Cochrane review concluded that there was insufficient high-certainty evidence to confirm the efficacy of omega-3 PUFAs

as a treatment for major depressive disorder (Appleton et al. 2021). More recently, a meta-analysis of 67 trials concluded that omega-3 PUFA supplementation significantly improved symptoms of depression in individuals with existing depression, with the greatest improvement observed at a dose of 1.5 g/day (Norouziasl et al. 2023). An umbrella review of 22 meta-analyses concluded that omega-3 supplementation had a significant impact on improving symptoms of depression when compared to placebo and recommended using this strategy as an add-on in management (Lu et al. 2023).

In dementia, it is widely believed that omega-3 polyunsaturated fatty acids (PUFAs) offer a promising nonpharmacological option to enhance cognitive abilities and decelerate the onset of dementia. The majority of the data supporting this concept come from epidemiological and preclinical investigations. Three randomized, placebo-controlled trials examining omega-3 polyunsaturated fatty acid supplementation in 632 individuals with mild-to-severe Alzheimer's disease (AD) over 6, 12, and 18 months were included in a Cochrane review. The Cochrane reviewers did not find any research looking into dementias of other kinds. For the majority of the outcomes, the overall quality of the evidence was strong (Burckhardt et al. 2016). There was no indication of any benefit from omega-3 polyunsaturated fatty acids. After 12 months of treatment, a very small research study (MD −3.50, 95% CI −4.30 to −2.70; 22 participants; moderate quality evidence) demonstrated a benefit for omega-3 PUFAs in instrumental activities of daily living.

Regarding the prevention of dementia, some studies have found no effect, whereas observational studies from the past have suggested that consuming more fish oils rich in omega-3 PUFA may lower the risk of dementia. This was investigated by a Cochrane review (Sydenham et al. 2012). Three randomized controlled studies with 3536 individuals were included by the authors. There was no statistically significant change in the mini-mental state assessment scores between the omega-3 PUFA and placebo groups in two investigations comprising 3221 people. Other measures of cognitive performance, including verbal fluency, digit span, and word acquisition, did not demonstrate any positive effects of omega-3 PUFA supplementation in two trials with a total of 1043 participants. Throughout the trials, participants in the intervention and control groups showed little to no cognitive deterioration. It is therefore concluded that there is no evidence that supplementing with omega-3 PUFAs improves cognitive function in older, cognitively healthy individuals. In addition, Omega-3 PUF supplements have not been shown to be effective in treating mild-to-moderate AD. This result held true for every outcome that matters to dementia patients. There is insufficient direct evidence linking omega-3 PUFs to incident dementia.

More comprehensive data is needed to support the possible benefits of PUFAs in schizophrenia and depression, and longer-term research projects are needed to uncover potential benefits of omega-3 PUFA supplementation in averting cognitive decline in the elderly. RCTs should particularly assess the ideal formulation and dosing of the omega-3 supplement, duration of use, as well as potential drawbacks.

18.4 Vitamins

The role of vitamins in mental health has exponentially evolved over the past decade. B vitamins have been of particular interest and have shown a benefit to general brain health and mood. The fundamental function of B vitamins as cofactors in different cellular activities, importantly the folate and methionine cycles, constitutes the basis for the hypothesis associating the levels of B vitamins with mood (Reynolds et al. 1984). By regulating the enzymatic reactions in the abovementioned cycles, B vitamins help contribute to the methylation of DNA and clearance of homocysteine (Kennedy 2016). When deficient, this disrupts the different metabolic pathways of the body and leads to a state of hyperhomocysteinemia (Otaegui-Arrazola et al. 2014). Research has supported the proposition that increased homocysteine levels are one risk factor for depression (Folstein et al. 2007; Esnafoglu and Ozturan 2020). Alternatively, through modulating one-carbon metabolism, B vitamins regulate dopamine and serotonin synthesis, further highlighting their intricate association with depression, as well as other psychiatric disorders (Young et al. 2019).

Clinically, a meta-analysis of 12 trials examining the effects of vitamin B supplementation (daily intake of three or more B group vitamins for at least 1-month duration) on mood in healthy and at-risk individuals found that it significantly reduced stress in both population groups, but did not impact depressive or anxiety symptoms (Young et al. 2019). Another meta-analysis of 8 trials noted significantly decreased levels of perceived stress, mild psychiatric symptoms, anxiety, fatigue, and confusion, but not depression following micronutrient supplementation. This was particularly observed when the intervention contained high doses of B vitamins (Long and Benton 2013). Another recent meta-analysis (20 trials; 2256 participants) also found that B vitamins significantly decreased symptoms of depression both as monotherapy and adjunctive to standard treatment, while vitamin D was effective in improving both depression and anxiety symptoms (Borges-Vieira and Cardoso 2023). In this section, the particular roles of vitamins B1, B9, and B12 are discussed. The section also highlights the clinical relevance of vitamin D supplementation in mental health.

18.4.1 Vitamin B1

Thiamine, or vitamin B1, has a major role in the maintenance of the central nervous system (Nishimoto et al. 2017; Dhir et al. 2019). Chronic alcohol drinking decreases thiamine's intestinal absorption by impacting membrane transport activity across intestinal epithelial cells (Subramanya et al. 2010). Wernicke's encephalopathy (WE), a life-threatening and severe condition in individuals with alcohol use disorder, occurs in this context secondary to alcohol-induced thiamine deficiency (Young 2014). WE manifests as ataxia, ophthalmoplegia, and altered mental status and can

lead to severe neurologic deficits, even death, if not treated (Ota et al. 2020). Intravenous thiamine is recommended for management wherein parenteral supplementation rapidly corrects the depletion and assists in reversing the associated neurologic symptoms (Lingford-Hughes et al. 2012). The British Association of Psychopharmacotherapy and the Royal College of Physicians guidelines recommend treating WE with parenteral doses of vitamin B1 greater than 500 mg/day for a duration of at least 3–5 days (Lingford-Hughes et al. 2012; Thomson et al. 2002). In light of the clinical controversy regarding the best thiamine supplementation regimen in WE, a recent literature review looked at the most appropriate replacement protocol. Regimes varied between intramuscular (up to 300 mg/day) and intravenous (100–1500 mg) formulations. All patients had improvement in their symptoms with no differences in outcomes regardless of the formulations. In addition, adverse side effects were minimal. The authors concluded that parenteral or intramuscular thiamine of at least 100 mg/day should always be provided for individuals with alcohol-induced WE (Smith et al. 2020).

18.4.2 Vitamins B9 and B12

Vitamin B9 (folate) and vitamin B12 (cobalamin) deficiencies have been associated with an increased risk of depression (Coppen and Bolander-Gouaille 2005). As such, research about supplementing as an adjunctive treatment for depression has been of increasing interest.

The role of vitamin B12 supplementation was investigated by Markun and colleagues in their meta-analysis of 16 RCTS with 6276 participants. They found that supplementation did not have any benefit in improving symptoms of depression or cognitive function (Markun et al. 2021). These findings were similar to an older meta-analysis that assessed the role of B9 and B12 vitamins in depression. Findings indicated that short-term use did not improve symptoms (based on 5 studies) although longer consumption (one trial) might be helpful (Almeida et al. 2015). However, one study of 6 RCTs particularly looking at folic acid or L-methylfolate supplementation as an adjunctive to antidepressants found that it improved scores on depression scale scores, response, and remission rates (Altaf et al. 2021). Furthermore, a meta-analysis covering 26,275 women (4 RCTs and 11 observational studies) concluded that folic acid supplementation during pregnancy significantly decreased the risk of perinatal symptoms of depression (Jin et al. 2022). A meta-regression also showed that prenatal folic acid consumption, particularly at a dose of at least 400 μg/day, was significantly associated with a reduced risk of autism spectrum disorder in newborns (Liu et al. 2022).

Regarding other mental health conditions, a meta-analysis of folic acid supplementation in schizophrenia found, based on 925 participants in 10 RCTs, that vitamin B9 significantly improved negative symptoms when combined with standard antipsychotic treatment. However, it did not have any impact on general, positive, or depressive symptoms (Sakuma et al. 2018).

Lastly, two systematic reviews looked at the role of adjunctive folate in major mental health conditions. One found an efficacy for supplementation in improving depressive symptoms in both unipolar and bipolar depression, as well as manic symptoms in bipolar disorder. However, no benefit was found in schizophrenia compared to placebo (Zheng et al. 2020). The other review highlighted the benefits of vitamin B9 in major depression, including postpartum and post-menopausal depression, bipolar disorder, schizophrenia, autism spectrum disorder, and attention-deficit hyperactivity disorder. The authors noted the need for further RCTs that use appropriate folate formulations, particularly levomefolic acid due to its unimpaired ability to cross the blood-brain barrier (Lam et al. 2022).

18.4.3 Vitamin D

Vitamin D's ability to pass through the blood-brain barrier, activate receptors, and regulate neurotrophic signaling and inflammation highlights its neuroprotective function in the context of mental well-being (Anjum et al. 2018).

An increasing amount of literature supports the link between vitamin D and depression, evident in lower serum levels in people with depression, the presence of vitamin D receptors in emotional control areas, and the role of this vitamin in the modulation of immune-inflammatory pathways (Menon et al. 2020). Although the directionality of this association remains unclear, research suggests that vitamin D consumption can have a therapeutic effect, particularly in individuals with major depressive disorder and comorbid vitamin D deficiency (Menon et al. 2020).

In that regard, one meta-analysis (4 trials; 948 participants) of oral/parenteral vitamin D supplementation vs. placebo found significant clinical benefits in reducing depressive symptomatology for the former group. The study also highlighted that the oral formulation was as effective as parenteral administration (Vellekkatt and Menon 2019). Another meta-analysis of 29 studies with 4504 participants found that supplementation led to not only an improvement in depression treatment but also a decrease in its incidence. These effects were noted when the daily dose of vitamin D was at least 2800 IU, the duration of the supplementation was at least 2 months, in case of vitamin D deficiency, female gender, and regardless of baseline symptoms of depression (Xie et al. 2022). In a recently published comprehensive meta-analysis encompassing 41 studies (53,235 participants; predominantly women), vitamin D supplementation also exhibited a significant capacity to alleviate depressive symptoms (Mikola et al. 2023). The effectiveness was particularly evident in individuals diagnosed with major depressive disorder and women experiencing perinatal depressive symptoms. Notably, this positive effect was not observed in healthy individuals without depression or major psychiatric or physical conditions. The effectiveness of vitamin D supplementation also varied based on factors such as the duration and dosage of supplementation. A shorter duration (less than 12 weeks) and doses over 4000 IU/day showed larger effects. Lastly, similar

outcomes were observed in people with both low (≤50 nmol/L) and sufficient (>50 nmol/L) baseline vitamin D levels (Mikola et al. 2023).

Other studies investigated the beneficial effect of vitamin D supplementation in children. A systematic review of 24 studies suggested a potential positive influence of adequate vitamin D consumption on the mental health of children (Głąbska et al. 2021). A meta-analysis of 4 RCTs analyzed the findings of 256 children supplemented with vitamin D in addition to methylphenidate for the treatment of attention-deficit hyperactivity disorder. The authors found a small but statistically significant improvement across all symptom domains (hyperactivity, inattention, and behavioral problems). However, the strength of evidence was low (Gan et al. 2019). In autism, one meta-analysis (3 trials; 203 children) concluded that vitamin D supplementation significantly decreased scores on the Social Responsiveness Scale (SRS) and Child Autism Rating Scale (CARS), suggesting improvement in symptoms of autism (Song et al. 2020). Another meta-analysis (5 trials; 349 participants) noted that supplementation was only beneficial for hyperactivity, but not for core symptoms of autism or coexisting conditions (Li et al. 2022a). The most recently published meta-analysis on the topic (8 trials; 266 children) noted that vitamin D significantly decreased stereotypical behaviors, as well as scores on SRS and CARS, but did not impact core symptoms and coexisting conditions (Zhang et al. 2023a).

The evidence for the efficacy of vitamin D supplementation seems to be most robust in certain groups of people with depression. Its role in other conditions, including autism, requires further RCTs with larger sample sizes and individualized supplementation regimens.

18.5 Minerals

Minerals, such as zinc and magnesium, serve various bodily functions. They possess antioxidant properties and act as cofactors of enzymes involved in metabolic reactions and neuronal conduction, among other roles (Shah et al. 2021). A review of the literature noted the positive association between a deficit in zinc and the risk of depression, as well as an inverse correlation between supplementing with zinc and depressive symptomatology. Hypothesized mechanisms include modulation of the hypothalamic-pituitary axis, the glutamatergic system, and inflammatory pathways (Wang et al. 2018). Less evidence was available for the role of other minerals, such as selenium and magnesium (Wang et al. 2018).

When looking at clinical data, a meta-analysis of three trials comparing zinc to placebo as adjunctive to conventional antidepressants showed preliminary evidence for the efficacy of the former in significantly decreasing scores of depression (Donig and Hautzinger 2022). Another meta-analysis of 5 trials also showed similar significant findings. In sub-analyses, the results were maintained in individuals with a mean age of 40 years and older (Da Silva et al. 2020). Alternatively, magnesium

supplementation was associated with a decrease in depressive symptoms in uncontrolled but not in placebo-controlled trials (Phelan et al. 2018). Another meta-analysis of 11 epidemiological studies found dietary magnesium consumption to be significantly associated with a decreased risk of depression; the largest risk reduction was found for doses of 320 mg/day (Li et al. 2017). Alternatively, based on two pooled trials, no significant effects on symptoms of schizophrenia were observed from supplementation with zinc or chromium (Firth et al. 2017). Findings highlight a potentially important role of zinc and magnesium in the management of depression (Szewczyk et al. 2018), but more studies are needed.

18.6 Amino Acids

Carbohydrates, fats, and proteins are the three major macronutrients of every diet. The latter and its constituent amino acids are essential to maintain cellular function and integrity. Research underscores the significance of protein intake, not only on physical health but also on cognition and mental status. This may be attributed to the fact that low protein consumption is associated with decreased intake of essential amino acids required for the synthesis of neurotransmitters (Glenn et al. 2019). Clinically, several trials highlighted the benefits of supplementing older adults with amino acids in terms of preserving brain function, reducing frailty, improving mood, and decreasing cognitive decline (Suzuki et al. 2020; Rondanelli et al. 2011).

In mental health, *N*-acetylcysteine (NAC), a supplement form of the amino acid cysteine, is the most studied nutrient, with data on its use in mood disorders, psychosis, and addiction, among other mental health conditions. In a meta-analysis of 5 trials looking at the effects of NAC supplementation on depressive symptoms across both unipolar and bipolar depression, NAC was associated with a significant decrease in depressive symptoms as compared to placebo, as well as in improvement in global and social functioning (Fernandes et al. 2016). A meta-analysis of 6 trials (248 participants) looking at NAC as an augmentation strategy in bipolar depression also showed a moderate effect size favoring it over placebo (Nery et al. 2021). Kishi and colleagues had different results in their review, wherein analysis of 7 trials (728 participants) concluded that NAC did not improve symptoms of depression in either major depressive disorder or bipolar depression (Kishi et al. 2020). Zheng et al. also looked at NAC use as adjunctive in major mental disorders and found positive effects in schizophrenia (3 trials; 307 participants), but not in bipolar or major depressive disorders (2 trials; 125 participants and 1 trial; 269 participants, respectively) (Zheng et al. 2018). A recent umbrella review of adjunctive agents to antipsychotics in schizophrenia concluded that NAC could help improve negative symptoms and general psychopathology on the Positive and Negative Syndrome Scale for schizophrenia whenever supplemented at a dose of 1200–3600 mg/day for at least 3 consecutive months (Fond et al. 2023). However, a recent meta-analysis found no benefit from adding NAC, as compared to placebo, in patients with psychotic disorders (8 trials; 594 participants) and recommended against its use in

routine clinical practice in the management of psychosis (Zhang et al. 2023b). On another note, a meta-analysis of NAC vs. placebo in 16 RCTs assessing substance use disorders showed a significant benefit from NAC in decreasing cravings, as well as in reducing withdrawal and depressive symptoms when considered as a single domain (Chang et al. 2021). In obsessive-compulsive disorder, a systematic review failed to show any benefit from NAC as an augmentation strategy in children and adolescents (Parli et al. 2023), while a meta-analysis highlighted potential promising results in adults (Gadallah et al. 2020). As findings on amino acids are limited and on NAC in particular inconsistent, further studies with larger sample sizes are needed to support the use of amino acids as an adjunctive in the treatment of psychiatric disorders.

18.7 Probiotics

The gut and brain communicate through intricate bidirectional pathways, including the central nervous system, autonomic system, and neuroendocrine and immune pathways (Carabotti et al. 2015). The hypothalamic-pituitary-adrenal (HPA) axis, which links the central nervous and endocrine systems and regulates the body's response to stress, is activated when the intestinal microbiota is disrupted. When the microbiota is diverse, the HPA axis regulates external stressors more efficiently. However, when it is less diversified, the axis becomes easily disrupted and poorly manages stressful situations (Madabushi et al. 2023). When this diversity is impacted, the gut's condition is referred to as dysbiosis. The dysbiotic state makes the cellular lining of the intestines permeable, allowing partially digested food components to enter into the blood, disrupting equilibrium and leading to inflammation. This process has been associated with the development of mental health conditions (Madabushi et al. 2023; Scriven et al. 2018). Besides, most neurotransmitters associated with depression, anxiety, and other mental health conditions, such as serotonin, dopamine glutamate, and gamma-aminobutyric acid (GABA), are also produced in the intestines (Madabushi et al. 2023, Scriven et al. 2018). As such, several mental health conditions have been linked to an imbalance of microbiota in the gut.

The effects of probiotics and prebiotics, their nutrient sources, were examined in the review by Ansari and colleagues, wherein the authors highlighted how *psychobiotics* might improve mental function via anti-inflammatory, antidepressant, and anti-anxiety functions. They also summarized the potential application of *psychobiotics* in different mental health conditions including major depressive disorder, anxiety, autism spectrum disorder, and Alzheimer's disease (Ansari et al. 2020).

The role of probiotics in depression has been highlighted for more than a decade now (Logan and Katzman 2005). The first meta-analysis of RCTs assessing probiotic-based interventions in the treatment of depression found that it significantly decreased depression scale scores in both healthy individuals and those with major depression. This effect was exclusive to people younger than 60 but not to

those aged 65 and above (Huang et al. 2016). Later, another meta-analysis of 19 RCTs (1901 participants) also showed a significant effect of probiotics in reducing depressive symptoms, in comparison to placebo, but only in patients with depression (no effect in those with other mental health conditions or in the healthy population) (Goh et al. 2019). Efficacy depended on the strains of probiotics used, highlighting the role of specific combinations or strains in management (Goh et al. 2019). The latest umbrella meta-analysis analyzing findings from 10 meta-analyses (8886 participants) confirmed that probiotics significantly decreased symptoms of depression compared to placebo. Findings were mostly robust for interventions of at least 2 months duration, using a dose of more than 10×10^9 colony-forming units of probiotics (Musazadeh et al. 2023).

In anxiety, Reis and colleagues concluded that probiotics reduced anxiety-like behaviors in a meta-analysis of 22 preclinical studies but did not reduce symptoms in humans (14 trials; 1527 individuals) (Reis et al. 2018). Another meta-analysis of 12 trials (1551 subjects) also showed no benefit from probiotics, compared to placebo, in decreasing anxiety symptoms (Liu et al. 2018). Two meta-analyses looking at trials of both depression and anxiety suggested a benefit from probiotics yet emphasized the low quality of evidence and multiple limitations of the included trials (Liu et al. 2019; El Dib et al. 2021).

There is a paucity of evidence on the role of probiotics in schizophrenia, and findings regarding their efficacy in managing psychotic symptoms are so far negative (Ng et al. 2019b; Minichino et al. 2021). In obsessive-compulsive disorder, research remains theoretical with no trials conducted yet (Kong et al. 2022). Three meta-analyses found no significant benefit from prebiotics or probiotics on symptoms of autism spectrum disorder (Rahim et al. 2023; Song et al. 2022; Ng et al. 2019a).

In conclusion, published trials and meta-analyses on psychobiotics highlight a potential and most consistent role in depression. However, in other mental health conditions, the impact appears to be limited. Further research including larger and more robust RCTs that consider the strain, formulation, concentration, and duration of supplementation of pre/probiotics is necessary to better evaluate their efficacy.

18.8 Others (St John's Wort, Valerian Root, and Ashwagandha)

18.8.1 St John's Wort

Belonging to the *Hyperaciae* family, St John's wort or *Hypericum perforatum* is a plant known for its marked antioxidant and antibacterial properties. Its extract has been used as a herbal remedy for various physical, neurological, and mental health conditions (Schempp et al. 2002). In psychiatry, most of the research about St. John's wort has been on depression, with multiple meta-analyses indicating a

potential clinical benefit. Several decades ago, Kim et al. found that St. John's wort is 1.5 times more likely than placebo to lead to an antidepressant response. Furthermore, it was equivalent to low-dose tricyclic antidepressants in the short-term treatment of mild-to-moderately severe depression (Kim et al. 1999). More recently, a meta-analysis of 27 trials (3808 patients) compared St John's wort to selective serotonin receptor inhibitors (SSRIs) in mild-to-moderate depression. The authors found that the former had a comparable response and remission rate to SSRIs and significantly lower discontinuation rates (Ng et al. 2017). Another meta-analysis looking at the same outcome in 27 studies (3126 patients) concluded that St John's wort did not differ from SSRIs in response, remission, or scores on scales for depression, although it did have a lower rate of adverse events. The authors deduced that both St John's wort and SSRIs can be equally effective in mild-to-moderate depression (Cui and Zheng 2016). This was reiterated by Apaydin and colleagues who noted, however, the heterogeneity of the evidence and its low quality, emphasizing the importance of interpreting such findings with precaution (Apaydin et al. 2016). One meta-analysis found that the evidence is inconsistent and confusing, as recent large trials suggested minimal beneficial effects compared to placebo, while older and smaller studies not restricted to patients with depression had positive results (Berner et al. 2005). The most recent meta-analysis on the topic was by Zhao and colleagues who analyzed 14 trials (2270 participants) looking at St John's wort use in comparison to SSRIs in adults. Findings supported the use of the supplement in mild-to-moderate depression, as it significantly decreased scores on depression scales while having fewer side effects (Zhao et al. 2023). Evidence supports a benefit for St John's wort in managing symptoms of depression, at least when mild to moderate. A holistic and personalized approach should be considered in case St John's wort is recommended in clinical practice.

18.8.2 Valerian Root

Valerian root has a detailed medicinal history going back to the first century AD (Bone and Mills 2012). Historically, it was harvested for its diuretic and carminative properties, among others, and it gained prominence in the Middle Ages for treating neurological disorders and insomnia (Bone and Mills 2012). Currently, valerian root extract is used over-the-counter worldwide for the management of stress, tension, sleep disturbances, and anxiety (Ross 2014). With over 200 valerian species available, *Valeriana officinalis* L. is the most recognized, regulated as a dietary supplement by the FDA in the United States and acknowledged by the European Medicine Agency for relieving mild nervous tension and sleep disturbances (Shinjyo et al. 2020).

The sedative and anxiolytic effects of valerian root are linked to valepotriates and valerenic acid, while its sleep-enhancing impact is associated with the upregulation of GABA receptors (Choi et al. 2018; Felgentreff et al. 2012). Moreover, valerian is

suggested to have mood-enhancing properties secondary to its influence on neurotransmitters such as serotonin and GABA (Felgentreff et al. 2012).

The effectiveness of valerian as a sleep agent has been a major focus of research. Various meta-analyses have been conducted, yet with inconsistent results. While some suggested positive outcomes (Fernández-San-Martín et al. 2010), others found methodological problems and inconclusive evidence (Stevinson and Ernst 2000; Taibi et al. 2007). The latest meta-analysis on the topic found inconsistent results for the benefits of valerian root on sleep quality and anxiety. The authors concluded that this is associated with the variation in the quality of the extract of the herb. They also suggested that more benefits would be seen when the whole root is used and if it is combined with other beneficial herbal supplements (Shinjyo et al. 2020). In conclusion, the current evidence does not support the use of valerian root as a sleep aid for insomnia.

18.8.3 Ashwagandha

Ashwagandha is a small shrub native to Africa, Central Asia, and South Asia. It is integral to Ayurveda, the ancient Hindu system of medicine, and is known for improving vigor by promoting muscle strength, endurance, and overall health (Ven Murthy et al. 2010). With over 50 chemical constituents, primarily withanolides (Mirjalili et al. 2009), Ashwagandha offers diverse therapeutic properties, from anti-inflammatory and antioxidant effects to anticancer and anxiolytic benefits (Singh et al. 2011). Its influence extends not only to neurological, endocrine, and cardiovascular activity but also to mental health conditions (Bano et al. 2015).

Highlighting findings of relevant trials, a 2-month study of adults with self-reported high stress showed that 240 mg/day of Ashwagandha, compared to a placebo, had significant anxiolytic effects and positively impacted cortisol and testosterone levels (Lopresti et al. 2019). In another trial of participants with schizophrenia, daily intake of 1000 mg for 12 weeks led to a significant reduction in depression and anxiety (Gannon et al. 2019). A 90-day study showed that Ashwagandha improved recall memory, focus, sleep, and stress levels compared to placebo (Gopukumar et al. 2021).

A systematic review of 41 studies looking at Ashwagandha's impact on various physical and mental health conditions concluded that the strongest evidence for its efficacy was in the domains of stress and anxiety symptoms (Lopresti and Smith 2021). One systematic review looking at the evidence of 5 trials assessing its role in anxiety noted that Ashwagandha led to greater improvement in anxiety compared to placebo, but studies were heterogeneous and of high risk of bias (Pratte et al. 2014). An updated meta-analysis on the topic (12 trials; 1002 participants) also found that it significantly reduced anxiety and stress compared to placebo (Akhgarjand et al. 2022). Alternatively, a meta-analysis of 5 trials (400 participants) supported Ashwagandha's beneficial effects on overall sleep, especially in insomnia, and when provided at a dose of at least 600 mg/day for a minimum of 2 months. No

serious adverse events were reported (Cheah et al. 2021). Overall, research suggests Ashwagandha's versatility in stress reduction and improvement of sleep disturbances. However, data on its serious adverse events are limited. Further high-quality studies are warranted, along with more safety data.

18.9 Discussion and Recommendations

While examining the aforementioned research findings regarding the use of various supplements in the management of major mental health conditions, one should keep in mind that the provision of any supplement should follow a personalized treatment approach. This should take into consideration various factors, such as the individual's unique characteristics, comorbid medical conditions including deficiency in certain nutrients and vitamins, coexisting psychiatric conditions, and the medication regimen being currently followed. Considering these elements, while keeping in mind the safety profile of the supplement and its potential side effects, is essential in formulating a comprehensive treatment plan and discussing it with the patient. In addition, open and transparent communication regarding the nutritional intervention, expectations and potential outcomes, and any associated risk factors is necessary to foster a collaborative approach and an informed decision-making process.

Supplements such as omega-3 PUFA, folic acid, NAC, and St John's wort exhibit substantial evidence in improving mental health, particularly depression. Others, including melatonin and thiamine, have established benefits in the treatment of sleep disturbances and WE, respectively. Other supplements, including vitamin B12, probiotics, and valerian root require further investigations that cater to the limitations of the currently existing trials. Overall, however, nutritional psychiatry holds promise as an adjunctive strategy in mental health care, providing an avenue to optimize the interplay between diet and mental health, as well as to improve the general well-being of the individual.

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Chapter 19
Diet and Sleep Disorders

Hagar F. Forsan

Abstract A dietary diet is thought to have a substantial sleeping well-being impact. A variety of dietary supplements have been utilized to improve sleep well-being. The link between sleep quality and dietary considerations, on the other hand, is difficult. Nutritional variables vary greatly with varied food patterns and are heavily influenced by everyone's digestive and metabolic roles. Furthermore, eating can have a significant impact on hormone levels and inflammation, both of which can lead to sleeplessness. This book chapter explains the function of critical nutrients, lipids, amino acids, vitamins, and carbohydrates pertaining to sleep and sleep problems. The intricate connection between diet and sleep also looks at the public and the clinical health insinuations of the available data. Sleep quantity and quality can be changed by dietary factors and nutrient intake that affect the regulation of hormonal pathways. Through biological and behavioral pathways, sleep influences the total consumption of energy in addition to certain meals and nutrients consumed. The primary focus of early studies in this area was on how inadequate sleep affects nutritional quality. Recent research, however, has looked at the dynamic connection between a poor diet and prolonged sleep. According to the most recent research, extremes in sleep length impact circadian rhythms, hormone levels, and sleep patterns, which affect outcomes related to weight and being obese, in addition to other factors for developing heart disease and type 2 diabetes. These routines could begin in childhood and affect a person throughout their entire life. Public health will be impacted by an improved understanding of the relationships between nutrition and sleep. As a result of the fact that noncommunicable illnesses are among the world's top causes of death, clinical environments are particularly crucial.

Keywords Nutrition · Diet · Sleep · Sleep quality · Sleep physiology · Sleep quantity

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Abbreviations

ALA	a-Linolenic acid
CVD	Cardiovascular disease
DHA	Docosahexaenoic acid
EPA	Eicosapentaenoic acid
GABA	Gamma amino butyric acid
GI	Glycemic index
IBD	Inflammatory bowel disease
LDL	Low-density lipoprotein
LNAAs	Large neutral amino acids
NE	Norepinephrine
OSA	Obstructive sleep apnea
PGD2	Prostaglandin D2
PGE2	Prostaglandin E2
PGs	Prostaglandins
PUFAs	Omega-3 polyunsaturated fatty acids

19.1 Introduction

The circadian rhythm, a biological cycle that repeats every 24 h in the body, is kept in balance. The daily regular physiological cycles are orchestrated by this typical circadian rhythm (Dibner et al. 2010). The normal circadian rhythm is disrupted by sleep disorders, which have a deleterious effect on both physical and psychological well-being (Pigeon 2010). There are numerous varieties of sleep problems, but the ones that are more frequently researched are obstructive sleep apnea (OSA), circadian rhythm abnormalities, and insomnia (Panossian and Avidan 2009). In addition to lowering life quality and productivity at work, sleep difficulties are also linked to more physical and mental health issues (Panossian and Avidan 2009). It is believed to raise the risk of developing certain disorders, including diabetes, especially type 2 (Brunner et al. 2008), hypertension (Sesso et al. 2003), and cardiovascular disease CVD (Ridker et al. 2003; Ridker et al. 2002). The health of children's sleep is related to their development of cognition, behaviors, and physical and mental health (Hysing et al. 2018). The biological clock's intrinsic genetic components (clock genes), as well as environmental influences like nutrition and environment, regulate the circadian rhythm.

It is thought that diet has a significant impact on how well we sleep (St-Onge e al. 2016b). The following pathways could be used to highlight the difficult subject of how nutrition affects sleep regulation. First, certain elements of a diet can directly impact sleep. For instance, the caffeine found in caffeinated coffee and tea increases the time needed to induce sleep while also reducing total sleep time and quality (Shilo et al. 2002).

Adenosine, a substance that induces sleep, shares chemical similarities with caffeine. Although various mechanisms may coexist, it is thought that caffeine operates

by temporarily blocking the brain's adenosine receptors (A2AR), which are responsible for producing sleep (Huang et al. 2011). Melatonin, a well-known sedative, provides the body with information about the daily cycle of light and dark. Two G-protein-coupled receptors, MT1 and MT2, are activated by melatonin to modulate its effects on circadian rhythm and sleep induction. Thus, melatonin-containing foods can directly affect sleep (Peuhkuri et al. 2012b). Second, numerous dietary metabolites may influence sleep in a direct or indirect manner by influencing other pertinent factors. It is crucial to keep in mind that nutrition may have a substantial impact on the commensal microbiota, which may have an impact on metabolite synthase (Gérard and Vidal 2019). Third, issues connected to long-term nutrition may change the condition of inflammation, which is also directly related to insomnia. Numerous studies have demonstrated that glucocorticoids and inflammatory cytokines are both elevated in those who have sleep problems, particularly C-reactive protein and interleukin 6 (Imeri and Opp 2009; Irwin et al. 2016).

The connection between dietary habits and levels of inflammation has already been examined (Galland 2010); therefore, it is no longer the main topic. It is important to note that this topic is attracting increasing amounts of study attention as a result of the discovery of the relationship between persistent inflammation and several of the most common illnesses in modern life. The impact of inflammation on sleep well-being is still an intricate issue that needs additional research. The amount of knowledge available has increased significantly during the last few decades about how diet and nutrition affect sleep. Nevertheless, many of these sleep research studies are descriptive in nature, have a small sample size, and produce inconsistent results. This raises the importance of investigations into the impact of various nutritional components based on clinical trials.

19.2 Amino Acids

The components of proteins are called amino acids. Numerous naturally generated amino acids exist, and the majority of them are consumed by humans. Numerous studies have been done in the last few decades on the impact of amino acids on insomnia and sleep quality.

19.2.1 Tryptophan

Serotonin is made from tryptophan, and its effects on sleep have been extensively researched for many years (Imeri and Opp 2009). One important sleep mediator, serotonin, initially makes people feel more awake and then eventually promotes paradoxical sleep, despite the fact that its function in sleep has been controversial (Imeri and Opp 2009). Tryptophan supplementation, particularly in people with mild insomnia, has been reported to increase subjective weariness and lessen the

time needed to drift off to sleep (Hartmann 1982). This is notably true in people with mild insomnia. Tryptophan was repeatedly shown to reduce latency for sleeping, which is correlated with blood pressure, in a random double-blind study on healthy individuals (George et al. 1989). Tryptophan consumption is important for kids to retain a morning-type attitude during breakfast maintain a healthy circadian rhythm and get enough sleep, according to a recent study of younger people in Japan (Harada et al. 2007).

19.2.2 Gamma-Aminobutyric Acid and Glutamine

Gamma amino butyric acid (GABA) is a bioactive amino acid that does not go into the formation of proteins. There are numerous studies demonstrating GABA's ability to promote sleep. Byun et al. published a trial of 40 individuals with insomnia who received GABA (300 mg/day) for 4 weeks and experienced reduced sleep latency and higher sleep efficacy (Byun et al. 2018). It has been documented how GABA works with its receptors to promote sleep (Gottesmann 2002). It has also been practiced to encourage sleep by using GABA receptor antagonists (Harrison 2007).

Additionally, glutamine is a non-essential amino acid that can be utilized to create GABA, an effective sleep aid and inhibitory neurotransmitter. As a result, it has been suggested and occasionally assumed that taking a glutamine supplement can help with sleep. However, since glutamine is not required, the body can produce it. The beneficial effects of supplementing with glutamine, if any, still require scientific verification.

19.2.3 Tyrosine

Norepinephrine (NE), a neurotransmitter, is the metabolite of the non-essential amino acid tyrosine. NE is released at its lowest amounts when you are sleeping and increases when you are awake. The fight-or-flight reaction, which causes the amount of NE to spike substantially in stressful or dangerous circumstances, is known as this phenomenon. NE has long been recognized for its function in sustaining overall arousal (Berridge et al. 2012), which has also been supported by studies utilizing animal models. Dopamine ß-hydroxylase knockout animals, which are deficient in norepinephrine, exhibited higher amounts of total sleep and required stronger cues to awaken after sleep restriction (Hunsley and Palmiter 2003). Through a1B-D4 and ß1-D4 receptor heteromers, NE dopamine's precursor, DA, also suppresses adrenergic receptor signaling and blocks the production of melatonin (González et al.

2012). Tyrosine supplementation has been utilized in numerous cognitive and behavioral investigations, although the outcomes have been noticeably inconsistent (Jongkees et al. 2015). Tyrosine supplementation of 150 mg/kg after an overnight sleep deprivation increased alertness, working memory, and reasoning according to Magill et al. (Magill et al. 2003). But nothing is known about how tyrosine supplements affect sleep disturbances. Tyrosine metabolites play important roles while sleeping.

19.3 Fatty Acids

Along with saturated and unsaturated fatty acids, fatty acids constitute an important part of the human diet. High saturated fat consumption raises levels of low-density lipoprotein (LDL) cholesterol and is linked to an increased risk of illness like diabetes and CVD (Hooper et al. 2020; Luukkonen et al. 2018). Among unsaturated fats, research on the impact of omega-3 polyunsaturated fatty acids (PUFAs), such as docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and a-linolenic acid (ALA), on human health has been substantial. Omega-3 PUFA consumption compared to saturated fat is proven to reduce the occurrence of CVD and stroke (Aung et al. 2018; Saber et al. 2017). Additionally, investigated and evaluated is the connection between fatty acids and sleep well-being (Yehuda et al. 1998).

19.3.1 Saturated Fatty Acids

Animal fat is virtually entirely made up of saturated fatty acids. Processed meals, especially those that are cooked in hydrogenated oil, are similarly high in saturated fatty acids. Many scientific organizations (Sacks et al. 2017) have recommended that diabetes and CVD are significantly influenced by saturated fat consumption. Saturated fatty acid research on sleep is uncommon. Increased saturated fat consumption throughout the day was linked to less slow wave sleep and higher alertness at night, according to research on normal weight people (Serio et al. 2023; St-Onge et al. 2016c). An additional investigation of 459 postmenopausal women examined the relationships between dietary elements and objective sleep. According to actigraphy, the scientists found an inverse relationship between total fat and saturated fat intake and total sleep time (Grandner et al. 2010). Consuming saturated fatty acids impairs sleeping health. Diabetes is caused by consuming saturated fatty acids for an extended period of time, as diabetes is usually connected with sleeping disorders (Surani et al. 2015).

19.3.2 Omega-3 Polyunsaturated Fatty Acid

Omega-3 PUFA is a polyunsaturated fatty acid (PUFA) with an outstanding health reputation. Fish and vegetables have a high amount of unsaturated fat in comparison to fats from animals, which are mostly saturated. The growth of the brain depends on omega-3 lipids. A DHA deficiency in the developing brain will cause issues with neurogenesis, which are linked to altered learning and visual issues (Innis 2008). A number of chronic diseases can be prevented by consuming omega-3 fats because they are also thought to be anti-inflammatory (Calder 2006). As a result, omega-3 fatty acids are often used as food supplements to prevent stroke and heart disease. A diet lacking in omega-3 PUFAs has been demonstrated in studies to disturb night sleep by interfering with the circadian clock and melatonin rhythm (Lavialle et al. 2008). According to research on healthy youngsters, having greater blood levels of DHA is linked to significantly better sleep healthiness (Montgomery et al. 2014). Adolescents were also shown to be affected by DHA in terms of sleep, as greater plasma DHA levels were linked to earlier bedtimes and extended weekend sleep (Jansen et al. 2020). While the majority of research found omega-3 PUFAs to be beneficial for sleep, one study found that after successful depression treatment, high-EPA fish oil supplements are likely connected to sleep disturbance; the symptoms went away following supplementation was discontinued (Blanchard and McCarter 2015). This unfavorable observation of omega-3 fatty acids is uncommon, nevertheless. Though fish is a good source of omega-3 fatty acids, there is conflicting evidence regarding how eating fish affects the sleep quality. In a group of people over 40, there is a link between getting enough sleep and eating fatty fish (Del Brutto et al. 2016). In addition, a research of 95 male adults from September through February, who consumed Atlantic salmon served three times a week, found a positive correlation between resting HRV, EPA + DHA, and daily functioning with regard to vitamin D status (Hansen et al. 2014). In comparison, there weren't any obvious variations in mental health or sleep of children aged 4–6 who consumed fish compared to those who consumed beef (Hysing et al. 2018).

19.3.3 Omega-6 Polyunsaturated Fatty Acid

Another kind of PUFA that is prevalent in vegetable oils like maize, soybean, and Primrose seed contains omega-6 PUFAs. Sleep advantages of omega-3 fatty acids are widely acknowledged, whereas the benefits of omega-6 fat are less well understood. Eicosanoids, which are powerful lipid mediators, are precursors to omega-6 fat. Arachidonic acid, for instance, is the starting point for a minimum of three lipid mediator classes, such as leukotrienes, thromboxanes, and prostaglandins (PGs) (Patterson et al. 2012). Eicosanoids obtained from omega-6 PUFA were frequently pro-inflammatory, whereas eicosanoids created from omega-3 PUFA were generally anti-inflammatory. It has been examined how omega-6 fatty acids metabolized and eicosanoids production affect inflammatory reactions (Patterson et al. 2012).

Prostaglandin D2 (PGD2) and prostaglandin E2 (PGE2) are crucial regulators of sleep because they are arachidonic acid prostaglandin derivatives. PGD2 has undergone experimental testing on various animal models to see whether it may effectively promote sleep (Inoue et al. 1984; Kantha et al. 1994). This humoral substance, as a sleep hormone, is distributed in the cerebrospinal fluid when the person is awake and progressively builds up in the brain. PGE2 has a potent waking impact and reduces sleep in rats, contrary to PGD2's sleep-inducing activity (Hayaishi 1988). Despite the fact that PGD2 and PGE2 are known to have a role in sleep regulation, research on how ingesting their omega-6 PUFA precursors affects sleep quality is lacking. In a bioinformatic investigation, reduced arachidonic acid biosynthesis was observed in the insomnia group, demonstrating that a higher incidence of insomnia may be connected with lower arachidonic acid synthesis. There has been no specific investigation into the effects of omega-6 fatty acids on sleep. In dietary intake, the ratio of omega-6 to omega-3 essential fatty acids (EFA) is often used to characterize fatty acid structure. While an ideal diet is thought to have an omega-6/omega-3 ratio of about one, this ratio has been increasing over time. A long time ago, the current ratio is 15: 1. The result of this imbalance has been linked to a variety of chronic inflammatory illnesses, including inflammatory bowel disease (IBD), obesity, CVD, rheumatoid arthritis, and nonalcoholic fatty liver disease (Patterson et al. 2012). Hundred people with Alzheimer's participated in a 4-week double-blind trial that discovered that taking a dietary supplement with a 4:1 ratio of omega-6 to omega-3 fatty acids improves sleep compared to a placebo (Yehuda et al. 1996)).

19.4 Carbohydrates

The influence of refined carbohydrates on illnesses is typically studied using the general glycemic index (GI) of food effect on postprandial levels of blood glucose (Neuhouser et al. 2006). Number of chronic illnesses, cancer (Kabat et al. 2008), and stroke (Yu et al. 2016) have all been linked to a high-GI diet (Barclay et al. 2008). When high-GI foods are consumed, blood glucose levels swiftly rise, causing an increase in insulin as a kind of compensatory and a cascade of subsequent humoral consequences. Studies on the impact of carbs on sleep have yielded conflicting findings. According to Afaghi et al., healthy sleepers (12 healthy people between the ages of 18 and 35) who consumed a carbohydrate-based high-GI lunch 4 h prior to bedtime experienced significantly shorter sleep onset latency (SOL, a 48.6% reduction) than those who consumed a low-GI meal (Afaghi et al. 2007). Another study's finding that a low-carbohydrate diet was linked to difficulties sleeping (Tanaka et al. 2013) is consistent with this conclusion. However, other research, like one just released by Gangwisch et al., advised that consuming high (GI) meals and load can raise the likelihood of experiencing insomnia (Gangwisch et al. 2020). This prospective study suggested that increased dietary added sugar, carbohydrate, and non-whole/refined grain intakes were linked to an increased prevalence of insomnia during a 3-year period in postmenopausal women. Over a 3-year period, higher

consumption of sugar and starches were each connected to a higher insomnia incidence in this prospective investigation on a considerably larger cohort of postmenopausal women. Additionally, they discovered that fruit that was not juiced and foods with higher fiber content were linked to lower incidence and insomnia prevalence. This result is in line with earlier research that discovered middle-aged Japanese female employees' poor sleep quality which is correlated with excessive intake of sweets (Katagiri et al. 2014). Tryptophan's proportion in the bloodstream to additional large neutral amino acids (LNAAs), for example, tyrosine, methionine, isoleucine, valine, leucine, and phenylalanine may change if a food has a high GI (Wurtman et al. 2003). It accomplishes this through the action of insulin, which was elevated after eating high-GI foods (Wurtman et al. 2003). Insulin encourages the muscles' preferential absorption of LNAAs, increasing the tryptophan ratio to LNAA. This ratio change may result in a rise in tryptophan levels in the brain (Afaghi et al. 2007) because tryptophan and LNAA compete for brain delivery (Oldendorf and Szabo 1976). Tryptophan is the building block of serotonin, which promotes sleep. After consuming carbohydrates, levels of serotonin could increase in the brain (Fernstrom and Wurtman 1971). The findings that a high-GI diet improves sleep were explained by this mechanism (Afaghi et al. 2007). This hypothesis, however, has been put into doubt by a recent study by Gangwisch et al., which showed that this idea may not be realistic because it requires the meal to only contain carbohydrates. Even 5% of the meal's protein content can stop tryptophan concentrations from rising (Gangwisch et al. 2020). Melatonin production, which is influenced by the existence of darkness, is not necessarily associated with an increase in serotonin (Gangwisch et al. 2020). Instead, they proposed that a high-GI meal may cause hyperglycemia and the compensatory hyperinsulinemia that follows as well as the release of growth hormone, glucagon, norepinephrine, and cortisol which worsens insomnia (Gangwisch et al. 2020; Gais et al. 2003). Furthermore, high-GI diets have been shown to affect gut flora and trigger inflammatory immunological responses (Kim et al. 2018), both of which may have a major effect on sleep quality (Gérard and Vidal 2019). The outcomes of the aforementioned research might be compared because they were conducted in various populations with radically varied sample sizes and experimental setups. However, additional study is necessary to investigate the link between a mechanistic view of insomnia and a high-carbohydrate diet.

19.5 Vitamins

19.5.1 Vitamin D

A fat-soluble vitamin called vitamin D is necessary for the body to absorb calcium and serves a variety of other biological purposes. The most crucial vitamins D3 and D2 can both be produced by the body when exposed to sunlight or consumed through diet (Alipouri et al. 2023). A significant source of dietary vitamin D is fatty fish. Several research has looked into how vitamin D affects sleep. Nine

studies—six cross-sectional, two case-control, and one cohort—were included in a meta-analysis to better understand the relationship between vitamin D and the risk of sleep disorders (Zhao et al. 2020). In general, the study found that a deficiency in vitamin D increases the risk of a number of sleep problems, including poor sleep quality, fatigue, and brief sleep duration (Zhao et al. 2020).

19.5.2 Vitamin C

The majority of citrus fruits and vegetables include vitamin C, which has been demonstrated to protect the brain from memory loss brought on by lack of sleep (Mhaidat et al. 2015). According to a study, those with shorter sleep durations perform worse than people with longer sleep durations. Short sleepers tend to ingest fewer vitamins, including vitamin C (Grandner et al. 2013). Long-sleepers have greater amounts of vitamin C in their plasma, according to cross-sectional research of persons in the UK. Intake of fruits and vegetables and sleep wellness may be associated (Noorwali et al. 2018). However, aside from that, the literature does not truly a wealth of data supporting the relationship between vitamin C and sound sleep.

19.5.3 Vitamin B6/B12

Pyridoxine, a form of vitamin B6 that is frequently present in food, is used as a coenzyme in many enzymatic processes. An examination of vitamin B6's effects and other B vitamins on no discernible changes was seen between the amount of time the B6-treated group and the placebo group spent awake at night, their sleeping habits' quality, or their level of fatigue when they woke up. On the other hand, the B complex-treated foods contain a lot of vitamin B6, which is used as a coenzyme in countless enzymatic processes. We investigated the effects of B vitamins on dreaming and sleep in a randomized, double-blind, placebo-controlled experiment. There were no discernible variations in the amount of time spent awake at night, the quality of their sleep, or their level of weariness between the B6-treated group and the control group. The effect of vitamin B12 on sleep is also up for debate. In case studies, vitamin B12 was suggested as a helpful treatment for a wake-sleep rhythm that ran amok and extended sleep phase disorder (Okawa et al. 1990). Intravenously injected vitamin B12 has a positive effect on rat sleep, particularly during the light period (Chang et al. 1995).

Prior to now, different lifestyle indicators for chronic disease have gotten more attention in clinical research, public health, and practice than sleep has. There are intricate mechanisms connecting nutrition and chronic illnesses risk to sleep length, quality, and behaviors. Currently, evidence points to a reciprocal relationship between nutrition and sleep length and quality. These aspects of sleep, together with how they interact with diet, affect the likelihood of getting a chronic illness. Here,

the main supporting evidence for these intricate interconnections is enumerated, the information on how dietary composition, foods that promote sleep, and diet quality affect sleep results. How much and how well you sleep can affect your chances of chronic diseases, such as type 2 diabetes, CVD, weight-related outcomes, and obesity are next considered. Examining the relationships between diet and sleep over the course of a person's life broadens this discussion. The implications of these findings for clinical practice and public health are then discussed, along with suggestions for future research initiatives (Frank et al. 2017).

19.6 Diet and Sleep

Behavior, sleep quality, and sleep duration are influenced by food composition, with a focus on specific dietary components (Grandner et al. 2013; Chauhan et al. 2023; St-Onge et al. 2016b). Shorter sleep duration has also been linked to protein and carbohydrate deficiencies (St-Onge et al. 2016b). A study found that eating high-GI carbohydrate meals 4 h before night shortened the time it takes for someone to fall asleep. An increase in tryptophan following carbohydrate eating was thought to account for this. Tryptophan is frequently cited as being significant in the hypothesized connections between nutrition and sleep since it is an amino acid source to the hormone serotonin, which regulates sleep (Peuhkuri et al. 2012a). Additional studies showed that evening dietary tryptophan intake enhances sleep in patients with sleep disorders and greater alertness in the morning, possibly as a result of higher sleep quality (Markus et al. 2005; Silber and Schmitt 2010). The consumption of micronutrients may also influence sleep patterns. Deficiencies in vitamin B1, zinc, iron, magnesium, folate, selenium, and phosphorus for instance have been linked to shorter sleep durations (St-Onge et al. 2016b), deficiencies in alpha-carotene, selenium, and calcium to sleep difficulties (Grandner et al. 2014). Low intakes of vitamin C and calcium are linked to poor restorative sleep, while low intakes of lycopene and vitamin D are linked to poor sleep maintenance (Rondanelli et al. 2011). Taking zinc, magnesium, and melatonin at night increased sleep quality in long-term care facility patients with insomnia (Rondanelli et al. 2011), while taking a vitamin D supplement improved sleep quality, latency, and duration in people with a sleep disorder (Majid et al. 2018). Another randomized, double-blind, placebo-controlled study in healthy persons found that zinc-rich meals boosted sleep onset latency and sleep efficiency over placebo, adding to the support for zinc. Moreover, a mouse study indicated that normal sleep regulation requires adequate magnesium levels, not levels that are above or below the clinically recommended range. Uncertainty still exists regarding the precise processes by which these micronutrients may influence sleep. As mediators of the associations between diet and disease, micronutrients have also been proposed (Kanagasabai and Ardern 2015). In contrast to vitamin C, which mediates the relationship between sleep duration and diastolic blood pressure, vitamin D and

carotenoids moderate the relationship between sleep duration and waist circumference or systolic blood pressure. Consuming foods and beverages that include stimulants has a comparable impact on certain aspects of sleep. Caffeine and theobromine are competing antagonists of adenosine, a hormone that regulates sleep-wake cycles (Ribeiro and Sebastiao 2010). Although caffeine and theobromine give off energy right away, additionally they have a lasting impact on sleep patterns that continue for a long time (Clark and Landolt 2017; Vorona and Ware 2002). These side effects include increased sleep latency, reduced total sleep time, reduced sleeping efficiency, lower perceived sleep quality, and REM sleep behavior disorder. Furthermore, alcohol, which is commonly used as a sedative, has an intricate influence on sleep. Due to its capacity to affect serotonin and norepinephrine levels, alcohol drinking decreases the latency of sleep and may disrupt sleep later in life (Roehrs and Roth 2001). There is proof that some entire foods impair sleep. As an illustration, kiwis, cherries, fatty fish, and milk have all been linked to better sleep outcomes (St-Onge et al. 2016b; Lin et al. 2011; Yamamura et al. 2009). These connections may be caused by the comparatively high levels of tryptophan present in some of these particular foods (Afaghi et al. 2007; Peuhkuri et al. 2012a). The amount of time that males spend sleeping has been favorably connected with their intake of bread, pulses, fish, and shellfish (Komada et al. 2017). Last but not least, there are data that suggest that alterations in daily food habits and eating behaviors may have an impact on certain aspects of sleep (St-Onge and Shechter 2014).

When ingested as part of food rather than as supplements, nutrients are likely to have a greater positive impact on overall health (Lentjes 2019). Despite this, little research has been done on how certain diets affect sleep quality in healthy people.

19.6.1 Chlorophytum Borivilianum (Root) and Velvet Bean

According to one study, taking a supplement containing chlorophytum borivilianum and velvet bean reduced sleep onset latency and increased subjective sleep quality, sleep duration, habitual sleep efficiency, and sleep disturbance scores when compared to those who did not take the supplement (McCarthy et al. 2012).

19.6.2 Aminobutyric Acid and Apocynum Venetum Leaf Extract

To find alterations in sleep indices, the amino acid-aminobutyric acid (GABA) and Apocynum venetum (herb) leaf extract (AVLE) were studied both separately and in combination compared to placebo (Yamatsu et al. 2015). GABA dramatically lowered the time until sleep began, but AVLE lengthened non-REM sleep, with only

minor effects on delta waves. These components did not work together to provide a synergistic effect.

19.6.3 Cherries

One study looked at how different cultivars of Jerte Valley cherries, which are imported from Spain, affected people's ability to fall asleep (Garrido et al. 2010). Due to differing levels of serotonin and melatonin, each cultivar's impact on sleep quality varied (González-Gómez et al. 2009). However, middle-aged subjects showed significant gains in terms of total sleep time, sleep efficiency, awakening frequency, total nocturnal activity, assumed sleep, and sleep start latency (Gonçalves et al. 2021).

The number of awakenings, immobility, and sleep onset latency all decreased in older persons while presumed sleep increased. The effects of consuming a Jerte Valley product including four blended cherry cultivars were investigated in a later trial in comparison to placebo controls in young, middle-aged, and elderly subjects. The middle-aged and older populations showed the greatest gains in a number of sleep indices, including higher actual sleep time and immobility, fewer awakenings, and decreases in sleep start latency (Garrido et al. 2013). Similar findings were found in another study looking at the ingestion of Montmorency tart cherry juice, which found that participants spent more time sleeping than napping and had higher total sleep efficiency scores than those who took the baseline and placebo (Howatson et al. 2012).

19.7 Sleep and Chronic Disease

Long (>9 h) and short (7 h) sleep durations may affect the likelihood of developing chronic diseases, according to mounting research (St-Onge et al. 2016a). Short sleep has drawn more attention and has been linked to a higher risk of type 2 diabetes, CVD, and obesity (St-Onge et al. 2016a); short sleep duration is thought to interfere with the body's restorative systems, resulting in biological and behavioral risk factors for the formation of chronic diseases (Arora et al. 2015). Sleep has an effect on the quantity of hunger signaling hormones in blood such as ghrelin and leptin (Broussard and Brady 2010). Lack of sleep causes levels of the satiety hormone leptin to drop while the hunger hormone ghrelin to rise.

Overeating may be caused by leptin and ghrelin hormone imbalance (Arora et al. 2015; Taheri et al. 2004). Teenage girls' sleep length has a detrimental impact on adiponectin, an adipose tissue secretory product, and increases brain activation in response to food cues, resulting in an increased desire for high-energy foods (Al-Disi et al. 2010).

Adiponectin levels drop when the hypothalamic-pituitary-adrenal axis is activated, whereas insulin and glucose levels rise is another way that heart failure sleep disorders and sleep deprivation contribute to metabolic dysregulation (Hirotsu et al. 2015). An increased risk for coronary heart disease, hypertension, and recurrent acute coronary syndrome has been linked to short sleep duration (Javaheri and Redline 2017), as well as higher sympathetic nervous system activity and inflammatory responses.

Another potential mechanism connecting short sleep patterns (such as shifting work and lack of sleep) and eating patterns (such as irregular and infrequent meal patterns) to outcomes related to weight is circadian disruptions (Ekmekcioglu and Touitou 2011). There are intrinsic circadian rhythms that influence hunger, satiety, and food-specific desire, as well as changes in energy expenditure brought on by sleep deprivation or recovery events, according to small laboratory studies with healthy persons (Sargent et al. 2016; Scheer et al. 2013). Additionally, men have been observed to consume more calories late at night and when their sleep is restricted, which makes them more prone to weight gain (Spaeth et al. 2014).

Short periods of sleep and poor quality of sleep are associated with higher energy consumption, a poorer diet, and imbalanced dietary behaviors, which can lead to weight gain (Chaput 2014; Dashti et al. 2015; Shi et al. 2008). Other suggested actions include increased eating options, psychological anguish, and more time more sensitivity to food rewards, unrestrained eating, and more energy requirements during prolonged awake, changes in hormones that influence appetite. In fact, folks who have trouble sleeping duration exhibit more erratic eating habits, including consuming more frequently, in smaller portions, and with more energy-consistent mealtimes.

Thus, lack of sleep may encourage excessive calorie intake by impacting food composition and eating habits. Shorter sleep duration is well-established to be associated with increased calorie and fat intake. Individuals who get 7–9 h of sleep per night consume more fat, indicating an antagonist dose-response relationship between sleep and dietary fat (Shi et al. 2008).

Although the link between weight and sleep increase has undergone extensive research and appears to be reliable (Patel and Hu 2008), its impact on weight loss is still unknown. Randomized clinical trials have shown that loss of weight and maintaining weight through food and lifestyle interventions can aid with sleep enhancements, despite the fact that these studies have mostly been done with people with pre-existing sleep disorders (Araghi et al. 2013; Johansson et al. 2009). Duration of sleep and weight reduction success were found to be directly correlated in one clinical investigation (Elder et al. 2012). However, more investigation is required to clarify the directionality of these correlations and determine whether getting more restful sleep could result in loss of weight among the general public.

There is growing evidence linking chronic disease to prolonged sleep periods, which are commonly characterized as lasting longer than 9 h (Buxton and Marcelli 2010; Furuncuoğlu et al. 2016). In trials and observational studies, a longer sleep duration has been linked to an increased risk of chronic kidney disease, obesity, type

2 diabetes, depression, and CVD (St-Onge et al. 2016a; Chaput 2014; Furuncuoğlu et al. 2016; Choi et al. 2017). The mechanisms underlying these associations, however, are unclear (Furuncuoğlu et al. 2016; Tsai et al. 2014). Given that these illnesses may result in sleep disturbances. Sleep apnea and sleep fragmentation, which are linked to prolonged sleep duration, may exhibit an unobservable reverse causation bias.

Research shows poor sleep quality and prolonged sleep duration are linked to higher cortisol reactivity and coronary heart disease incidence (Ferrie et al. 2007; Song et al. 2016). Variations in sleep duration may increase the risk of metabolic syndrome, type 2 diabetes, CVD, and all-cause mortality. Frequent shift rotations in workers contribute to increased inflammation and sleep deprivation (Sonati et al. 2016; Viitasalo et al. 2015).

19.8 Diet and Sleep Throughout Life

Early in life and during the course of one's life, it becomes clear that diet, sleep, and risk factors for chronic disease have a complicated relationship (Dunk et al. 2023). Early childhood is when the influence of dietary content on sleep patterns was first noticed. In a cohort of 1- and 2-year-old babies, higher calorie intake after the evening meal was associated with longer hours of sleep (Diethelm et al. 2011). Influence of biological risks, especially leptin and ghrelin dysregulation, that raise the risk of chronic diseases is also highlighted by studies on sleep patterns in children. A long-term research investigation that looked at length of sleep and leptin found a link between chronically short periods of sleep and lower leptin levels later in childhood. This association was even stronger in girls with higher body obesity (Boeke et al. 2014). Additionally, there is proof that eating habits affect kids' sleep. According to a cross-sectional study (Khan et al. 2017), kids who eat in between meals or after dinner have shorter and lower-quality naps. Additionally, children who sleep for shorter period of time have a higher chance of becoming obese (Iglowstein et al. 2003).

It is comparable to the trend reported in young infants that adolescents who report short periods of sleep have elevated ghrelin and relatively low leptin levels (Taheri et al. 2004). Teenagers are now most likely to experience insufficient sleep (68.9%), and they are also more likely to experience short sleep durations (Iglowstein et al. 2003). This finding may be explained by a number of distinctive behavioral risk causes, for example increased use of electronic devices and poor dietary habits (Frank et al. 2017; Weiss et al. 2010).

72% of teenagers admit to using an electronic device "constantly," and 72% admit to using their cellphones in bed while attempting to fall asleep (Weiss et al. 2010). Reduced physical activity, unhealthy eating habits, and worse sleep quality have all been linked to increased screen time (Christofaro et al. 2016; Pyper et al. 2016). Teenagers who sleep less than 8 h per night consume fewer fruits and vegetables, consume more fast food, and consume more fat (Kruger et al. 2014). This

leads to a higher percentage of energy from fat and a lower percentage from carbohydrates. Adolescents may develop eating habits that increase the risk of sleep disorders and chronic disease (Mulligan et al. 2011). Most of research on the relationship between nutrition and sleep has been conducted on healthy, young, or middle-aged people.

There is little research on the relationship between nutrition and sleep among older people or in groups of people who already have health issues. The little research done with senior populations confirms what was discovered in younger populations. Poor sleep in the elderly has been linked to type 2 diabetes, obesity, metabolic syndrome, and hypertension (Chiang et al. 2014; López-García et al. 2008). However, because many of these research investigations are cross-sectional and older people are already more likely to develop certain illnesses, problems of reverse causality are especially pertinent in these populations.

19.9 Implication for Clinical Practice and Public Health

According to the National Sleep Foundation, the average American's diet quality and sleep duration are both subpar and have been falling over time (Iglowstein et al. 2003; National Sleep Foundation 2014). Moreover 50% of American children and 42% of American adults reported getting insufficient sleep in 2010. The percentage of Americans who adhere to five healthy living behaviors fell from 15% in 1988 to 8% in 2006 (King et al. 2009) as a result of this concurrent fall in risk factors for chronic disease that may be influenced by sleep. The trends in the United States are consistent with worldwide patterns of reported sleep problems and a shift toward unhealthy lifestyle behaviors, particularly in low-income Asian and African nations (Stranges et al. 2012).

These changes highlight the importance of translating known scientific data on the relationship between diet and sleep patterns into messages, initiatives, and interventions that the general community can easily understand and utilize to prevent chronic disease (Wilson et al. 2022). The National Sleep Foundation (Hirshkowitz et al. 2015) has made age-specific, research-based sleep time advice available in the United States. The American Academy of Sleep Medicine has also issued pediatric and adult sleep time recommendations (Panel et al. 2015; Paruthi et al. 2016). The 2015 Dietary Guidelines for Americans provide recommendations for exercise and other aspects of maintaining a healthy lifestyle, but they leave out advice on the critical relationship between nutrition and sleep (You 2015). Given the growing body of research, information on sleep should be included in further revisions of the Dietary Guidelines for Americans to strengthen their recommendations for leading healthy lives. Similar to this, international organizations and other nations may devote more funds to this issue in order to offer advice on diet and sleep to the entire population.

Additionally, initiatives should be made to include sleep-related material in contemporary multidisciplinary nutrition and other important aspects of health. The

early research in this field has shown promise. For instance, participants in a community-based wellness intervention saw increases in nutritional quality, sleep duration, and indications of obesity (Tomayko et al. 2017). In the first 2 years of a child's life, obesity was prevented by an intervention to avoid unfavorable sleep behaviors in pregnant women (King et al. 2009). The most encouraging part is that people from different socioeconomic and cultural backgrounds have shown these benefits (Tomayko et al. 2017; Mantziki et al. 2014). The way sleep and nutrition are approached in the clinical context may benefit from additional tactics. In order to identify at-risk patients and provide them with counseling, healthcare professionals should be trained and educated about the link between diet and sleep, especially those who work with at-risk populations. Quick, validated screening tools should also be developed and used to assess diet composition, eating habits, and sleep patterns. Finally, novel, integrative treatments should be developed that take into account the significant links between diet and sleep. For diseases like sleep apnea and sleep fragmentation, which are afterward linked to prolonged sleep duration, there may be an unobservable reverse causation bias.

19.10 Conclusions

Nutrition, meal schedule, and sleep have a symbiotic relationship because the circadian rhythm influences the metabolic profile and changes in metabolic and nutritional status influence the circadian rhythm. Consuming high CHO meals, tryptophan, melatonin, and phytonutrient-rich foods (like cherries) potentially increase the amount and your sleep quality. Although more research is needed to completely comprehend the processes behind many of these impacts, it is likely due to dietary factors that affect the actions of serotonin and melatonin. Future study should make sure that the dietary metrics used are consistent and use both objective (e.g., PSG/EEG) and subjective assessments to increase and improve the accuracy of the data and allow for accurate comparisons between studies and established sleep evaluation/methodologies. Changes in the levels of melatonin, cortisol, ghrelin, and leptin in the blood are regularly linked to poor sleep, but it is possible that there are other contributing factors as well. Additionally, links between little sleep, a lot of total calories consumed, and a poor diet have been discovered. Short sleepers frequently exhibit erratic eating patterns and consume their main meal later in the day. Visceral disorders may be caused by sleep problems or sleep deprivation, which in turn may be a symptom of an illness. Shorter, lower-quality sleep is frequently a side effect of chronic digestive illnesses.

However, the majority of the data are drawn from subpar studies. Therefore, to confirm causal relationships, epidemiological studies with sufficient power and controlled research targeting chronic short sleepers are required. Sleep extension studies incorporating patients with GI illnesses are also necessary to shed information on the association between GI issues, nutrition, and sleep quantity and quality. It is therefore advised to use an integrated approach that involves

gastroenterologists and sleep specialists, using verified surveys and the ICSD-3 classification defines and categorizes the specific sleep routine that is impacted by or associated with GI disorders. In fact, a multi-specialist strategy could clarify the complex, bidirectional relationship between GI tract diseases and sleep problems and, maybe, help uncover new treatment targets aimed at enhancing patients'quality of life.

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Chapter 20
Nutritional Interventions vs. Pharmacological Interventions

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Abstract This book chapter critically compares the efficacy, mechanisms, and implications of nutritional interventions vs. pharmacological interventions in the management of various psychiatric disorders. It explores the growing body of evidence supporting the therapeutic potential of dietary modifications, supplementation, and nutraceuticals in preventing and treating diseases, alongside traditional pharmacological approaches. The chapter evaluates the strengths and limitations of each approach, highlighting their respective roles in promoting health and combating illness. Furthermore, it examines emerging concepts such as personalized nutrition and integrative medicine, which integrate both nutritional and pharmacological interventions to optimize patient outcomes.

Keywords Nutritional interventions · Pharmacological interventions · Dietary modifications · Supplementation · Nutraceuticals · Health promotion

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20.1 Introduction

Nutritional and pharmacological interventions have significant roles in the treatment of different diseases including psychiatric disorders (Offor et al. 2021; Ros and Carrascosa 2020). There is a direct link between diet and mental health (Godos et al. 2020). Psychiatric patients' health can be improved by nutritional interventions that lower meal caloric content (Casagrande et al. 2011). According to the self-reported dietary patterns of acute psychiatric inpatients, 75% of these patients consume unhealthy diets. The results point to the possibility that better eating practices, such as a Mediterranean diet, may have a positive effect on eliminating symptoms and stabilizing acute symptoms in an inpatient setting for a short time (Gill et al. 2021). For many psychiatric disorders, pharmacological therapies are the cornerstone of care. They function by altering the brain's neurotransmitter levels, which are molecules that facilitate communication between nerve cells (Vollenweider and Preller 2020; Kato et al. 2013). Nutritional interventions can be used in combination with pharmacological interventions to offer more effective treatment for psychiatric disorders.

20.2 Schizophrenia

Schizophrenia (SCZ) is a chronic and serious mental condition that impacts an individual's thinking, feelings, and actions. Antipsychotic drugs are the mainstay of treatment for SCZ (Maric et al. 2016). Nevertheless, they are accompanied by notable metabolic adverse effects (De Hert et al. 2011), which increase the likelihood of metabolic syndrome, type 2 diabetes, and cardiovascular disease (CVD) in individuals. Significantly, CVD is the main factor leading to early death in individuals with severe mental illness, reducing their life expectancy by 11–20 years (Hennekens et al. 2005; Rajkumar et al. 2017). Although clozapine and olanzapine are associated with the greatest metabolic risk (Musil et al. 2015), all antipsychotics cause weight gain in younger individuals who have had limited prior exposure to these drugs (Fig. 20.1) (Alvarez-Jiménez et al. 2008). In addition, irrespective of their classification, these drugs autonomously increase the susceptibility to type 2 diabetes in persons with SCZ (Rajkumar et al. 2017).

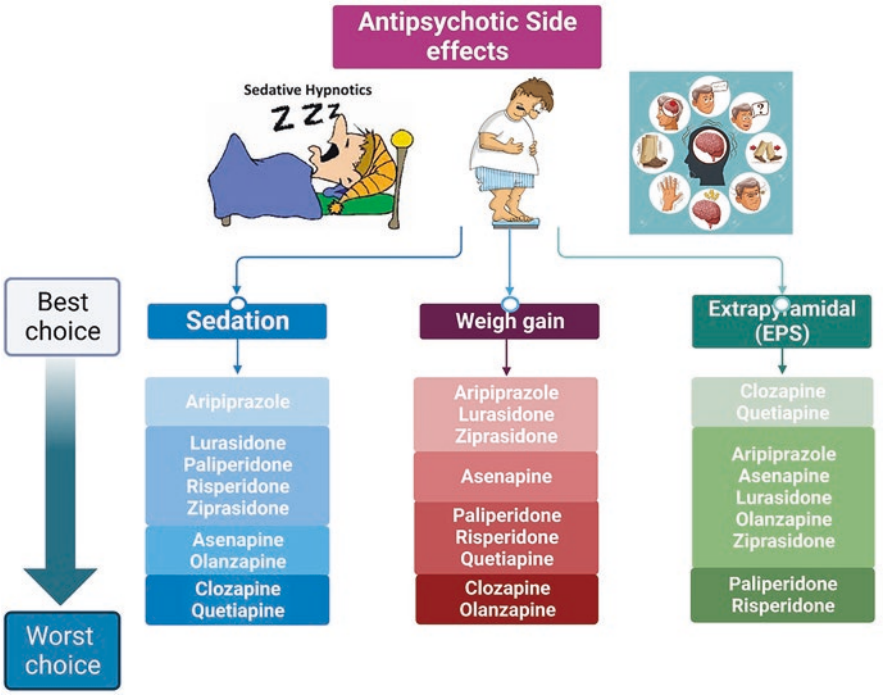

Fig. 20.1 Common side effects of anti-psychotic drugs

The use of nutritional supplements, including vitamins and trace elements, has garnered significant interest as potential therapeutic targets or complementary treatments in managing schizophrenia.

20.2.1 Role of Diet Rich with Antioxidants and Amino Acids in the Management of Schizophrenia

Oxidative stress plays a crucial role in SCZ's development, interlinked with processes like inflammation, mitochondrial dysfunction, lipid peroxidation, apoptosis, and DNA mutations (Choi et al. 2023). As a result, dietary antioxidants are being considered as supplementary therapy for SCZ. L-theanine, a natural antioxidant, has shown inhibitory effects on lipid peroxidation (Saleem et al. 2017). Furthermore, dysfunction of the N-methyl-D-aspartate (NMDA) receptor has been

implicated in SCZ pathogenesis. Therefore, certain amino acids acting as NMDA receptor agonists, like D-serine, glycine, and D-cycloserine, have demonstrated improvement in the negative symptoms of SCZ (Panizzutti et al. 2019).

Amino acids play imperative roles in SCZ treatment due to their involvement in neurotransmitter synthesis. For instance, tyrosine serves as a dopamine precursor, while tryptophan contributes to serotonin production, both are major neurotransmitters involved in SCZ pathogenesis. Numerous studies have highlighted the significance of amino acids in SCZ treatment. For instance, L-lysine administration improved positive symptoms of SCZ (Wass et al. 2011). Additionally, administration of L-theanine and N-acetyl cysteine has shown reductions in positive symptoms among SCZ patients (Arroll et al. 2014).

20.2.2 Role of Diet Rich with Fatty Acids in the Management of Schizophrenia

Omega-3 fatty acids, well known for their anti-inflammatory properties, have been proposed to alleviate symptoms associated with SCZ. These nutrients play a pivotal role in suppressing nuclear factor kappa B, a regulator of inflammatory responses (Calder 2017), and exhibit anti-inflammatory effects by reducing pro-inflammatory cytokines like IL-1, IL-6, and TNF-α (Albracht-Schulte et al. 2018). Studies have indicated reduced levels of docosahexaenoic acid (DHA) and α-linolenic acid, Eicosapentaenoic acid (EPA) and DHA in individuals suffering from SCZ (Peet 2008).

Research involving omega-3 fatty acid treatment for 12 weeks showed decline in plasma TNF-α levels accompanied by reduced triglyceride levels in schizophrenic patients with metabolic syndrome (Xu et al. 2019). Additionally, apart from traditional SCZ symptoms, recent findings have focused on other complications or side effects related to antipsychotic drug usage. Omega-3 fatty acids have demonstrated an improvement in cognitive functions among individuals with schizophrenia and metabolic syndrome. This improvement coincided with increased brain-derived neurotrophic factor levels and reduced levels of pro-inflammatory cytokines CRP, IL-6, and TNF-α (Tang et al. 2020). Overall, compelling evidence supports the idea that omega-3 fatty acids partially alleviate symptoms of SCZ through their anti-inflammatory properties.

20.2.3 Role of Diet Rich with Vitamins in the Management of Schizophrenia

Numerous epidemiological studies have linked low maternal levels of vitamin D to an increased risk of SCZ. Notably, prenatal and postnatal vitamin D supplementation has shown promise in decreasing the likelihood of developing SCZ later in life

(McGrath et al. 2004). Individuals born in winter and spring seasons, with reduced levels of vitamin D, exhibit a higher risk of SCZ (Heaney et al. 2003). Additionally, studies have highlighted those individuals with darker skin, leading to higher melanin concentrations, are more prone to vitamin D deficiency, potentially elevating the risk of developmental vitamin D deficiency in their children (Eyles et al. 2003). Finnish male children receiving appropriate vitamin D supplementation during their first year of life showed a reduced likelihood of developing SCZ (McGrath et al. 2004). Infants with low vitamin D concentrations face a twofold increased risk of SCZ later in life (McGrath et al. 2010). Vitamin D therapeutic efficacy is attributed to its impact on inflammatory molecules like TNF-α and IL-6 (Cha and Yang 2020). This evidence collectively suggests that developmental vitamin D deficiencies may heighten the risk of SCZ, yet further research is required.

A meta-analysis has identified lower levels of vitamins B6, B8, and B12 in schizophrenic patients compared to the control group. However, no noticeable effect of supplementation with B vitamins was observed on the negative nor positive symptoms of SCZ (Firth et al. 2017). Vitamin C, an antioxidant known for its role in inflammation protection, demonstrated associations with SCZ symptoms in Korean patients, alongside low intake of vitamin B3 and B9 (Kim et al. 2017). Administering vitamin B9 as an adjuvant therapy to antipsychotic drugs may hold benefits for patients with a genetic vulnerability (Roffman et al. 2013). In specific studies, vitamin C given at a dose of 200 mg per day for 8 weeks displayed significant improvements in ascorbic acid levels and minimal psychiatric rating scale scores, suggesting enhancement in psychopathological status (Brown and Roffman 2014). Co-administration of vitamins E and C also showed reductions in various psychiatric scores in SCZ patients treated with haloperidol (Sivrioglu et al. 2007).

20.2.4 Role of Diet Rich with Minerals in the Management of Schizophrenia

It has been observed that patients with SCZ showed a high level of magnesium in their blood. The magnesium level was reduced after treatment with haloperidol (Botturi et al. 2020). Also, calcium levels in schizophrenic patients were elevated compared to controls (Berridge 2014). Furthermore, low levels of iron, sodium, potassium, and selenium have been reported in patients with SCZ (Uddin et al. 2021). As dopamine disruption is implicated in the pathogenesis of SCZ, copper elevation may be related to dopamine dysregulation. A higher level of copper has been found in schizophrenic patients as compared to controls. In line with this result, a previous study reported an elevation in the copper level of SCZ patients along with a reduction in manganese and iron levels relative to controls. However, the plasma levels of selenium and zinc did not vary between groups (Baj et al. 2020). A recent study revealed that decreased level of zinc in SCZ patients was observed in relative to controls (Joe et al. 2018). Another clinical study demonstrated that treatment with zinc for 6 weeks ameliorated the symptoms of SCZ as compared to controls (Petrilli et al. 2017). Meanwhile, a previous

research displayed that maternal iron deficiency increased the susceptibility to SCZ in the offspring (Sørensen et al. 2011). Consequently, more research is required to understand the therapeutic potential of minerals in both SCZ pathogenesis and managment.

20.3 Depression and Mood Disorders

Mood disorders, such as Major Depressive Disorder (MDD) or depression, are common psychiatric diseases that greatly affect individuals' quality of life. The monoamine systems are greatly linked to stress resilience and the pathophysiology of mood and mood disorders. Consequently, tricyclic antidepressants which inhibit serotonin and noradrenaline reuptake, and selective serotonin reuptake inhibitors (SSRIs) are commonly prescribed for the treatment of these disorders. These agents also exhibit a limited extent of dopamine reuptake inhibition. While antidepressant drugs are generally considered beneficial, their uncontrolled intake poses certain risks. For instance, when taken at a young age, these drugs may impact brain development and elevate the risk of suicide (Olivier et al. 2011). Moreover, the triple inhibition of monoamines reuptake of serotonin, norepinephrine, and dopamine mimicks the pharmacological action of cocaine, which is a potent psychostimulant with abuse potential (Estave, Albertson, Karkhanis, & Jones, 2024). In addition to monoamine reuptake inhibitors, drugs that impede the breakdown of monoamines, particularly monoamine oxidase A (MAO-A) inhibitors, are utilized to enhance mood (Chamberlain & Baldwin, 2021). However, these agents come with substantial side effects, with the serotonin syndrome being a major risk, as excessively high serotonin levels can be toxic (Edinoff et al. 2021). Thus, while monoamine reuptake and MAO-A inhibitors can improve mood, especially in individuals with a low mood state, their use is associated with multiple risks (Chamberlain & Baldwin, 2021).

20.3.1 Nutrients and Mood Changes

Several epidemiological studies have unveiled links between dietary patterns and mood. Notably, a Western-style diet, characterized by high consumption of processed foods and sugar while lacking in fruits and vegetables, has been associated with deteriorating mood states. An included study observed heightened depression scores among individuals on a high glycemic load diet (Breymeyer et al. 2016). Conversely, diets abundant in carbohydrates but low in fat and protein have shown associations with lower mood scores in various cross-sectional studies (Pellegrin et al. 1998). In this part, we shed the light on the role of dietary nutrients in mood related disorders. Dietary nutrients are broadly categorized into two main types: macronutrients and micronutrients, with the latter further divided into four distinct types, namely vitamins, macro-minerals, trace minerals, and organic acids.

20.3.1.1 Micronutrients

Micronutrients are vital for the proper functioning of both the central and peripheral nervous systems. Inadequate intake of various micronutrients has been associated with a heightened risk of experiencing depression (Muscaritoli, 2021). This encompasses deficiencies in essential vitamins such as B6, B12, D and folic acid, along with crucial minerals like zinc and magnesium. Recognizing and addressing these deficiencies in individuals with depression is critical for effective management (Kiani et al. 2022).

Vitamins

The B Vitamins, comprising eight water-soluble molecules, serve as essential enzymes in metabolic pathways and are abundant in unprocessed foods. Deficiencies in these vitamins can lead to various chronic conditions such as anemia, peripheral nervous system impairment, and severe mental disturbances (Calderón-Ospina & Nava-Mesa, 2020). Depressive symptoms are notably associated with deficiencies in specific B vitamins like B12, B6, and folic acid (Markun et al. 2021). Research suggests that higher intake of vitamin B12 and folate is associated with a reduced risk of depression, yet it is uncertain if adequate intake can prevent its onset. Deficiencies in vitamin B12 and folate disrupt a metabolic process called one-carbon metabolism, causing elevated homocysteine levels and reduced S-adenosyl methionine, a critical methyl donor for neurotransmitter synthesis like serotonin, dopamine, and norepinephrine. Lower S-adenosyl methionine levels are commonly observed in individuals with depression (Cuomo et al. 2020). Elevated homocysteine levels can lead to the production of neurotoxic agents, potentially over activating specific brain receptors associated with depression. Depression has been linked to low B vitamin levels and/or high homocysteine levels in the general population, with vitamin B12 showing a strong correlation in older individuals (Robinson et al. 2011).

Further, deficiencies in folate or vitamin B12 have significant implications in the development of MDD by elevating homocysteine levels, which in turn impacts vascular responses (Hoepner, McIntyre, & Papakostas, 2021). Studies often reveal that individuals with MDD tend to exhibit lower concentrations of serum or red cell folate. Additionally, poor folate status and lower dietary folate intake have been correlated with the severity of depressive symptoms and prolonged episodes of MDD (Liwinski & Lang, 2023). This underscores the potential role of these nutrients in the manifestation and persistence of depression.

Foods containing vitamin B6 encompass a wide array of options, including poultry, seafood like tuna and salmon, beef liver, dairy products like milk and cheese, legumes such as lentils and beans, leafy greens like spinach, carrots, brown rice, bran, sunflower seeds, wheat germ, and whole-grain flour. Remarkably, these foods also serve as sources of tryptophan, a precursor to serotonin, contributing to the body's serotonin production (Shabbir et al. 2013).

Vitamin C, known for its potent antioxidant properties, has shown promise in mitigating oxidative stress. High-dose ascorbic acid supplements, at around 3 grams per day, have been associated with potential reductions in the severity of MDD and depressive scores (Das et al. 2021).

Vitamin E serves as a crucial lipid-soluble antioxidant that shields neuronal membranes from peroxidation (Usman et al. 2023). Research has indicated that individuals with MDD often exhibit lower serum concentrations of vitamin E compared to healthy counterparts, and this deficiency may correlate with the duration of the condition. Moreover, the positive effects observed from vitamin E supplementation in MDD are thought to involve the modulation of neuro-inflammation and oxidative stress (Manosso et al. 2022).

Vitamin D operates as a steroid hormone essential for calcium absorption, bone health, and mental well-being. Its synthesis is triggered by exposure to ultraviolet B light, and can also be obtained through dietary sources. To become biologically active, the molecule undergoes initial hydroxylation in the liver, followed by a secondary hydroxylation process occurring in the kidneys, brain, and immune system (Borges et al. 2011).

Vitamin D deficiency often stems from inadequate exposure to sunlight and insufficient intake of this essential vitamin. This insufficiency can lead to understimulation of brain receptors, potentially contributing to depressive symptoms. Cross-sectional studies have frequently associated low serum vitamin D levels with depressive symptoms (Cashman, 2020). Some findings suggest that vitamin D supplementation might influence the inflammatory and oxidative processes, particularly in a subset of individuals responding to treatment for MDD. However, the current evidence doesn't strongly support vitamin D supplementation alone or as an adjunctive therapy for improving depressive symptoms. Intriguingly, a meta-analysis indicated positive effects of adjunctive vitamin D supplementation among individuals with major depression, especially those with concurrent vitamin D deficiency (Lee et al. 2011).

Magnesium

Magnesium plays a vital role in more than 300 cellular processes within the body and contributes significantly to inflammatory defense mechanisms. Deficiency in magnesium can lead to heightened NMDA activity, potentially resulting in depressive symptoms and neuroendocrine alterations (Pickering et al. 2020). Studies have shown lower serum magnesium levels in adults diagnosed with depression. While the specific role of magnesium in preventing depression remains unclear, maintaining a healthy dietary pattern is often recommended to ensure sufficient magnesium intake (Zarate et al. 2013).

Selenium

Selenium holds significance as a mood regulator, yet the precise mechanisms behind its impact on mood remain unclear. This mineral plays a pivotal role in synthesizing and metabolizing thyroid hormones. A deficiency in selenium can disrupt thyroid hormone metabolism, potentially contributing to depressive symptoms. Moreover, selenium deficiency often compromises immune function, a common occurrence in individuals with MDD. Furthermore, selenium is crucial for the antioxidant enzyme glutathione peroxidase, thus safeguarding nerves against lipoperoxidation and tissue damage. Studies indicate that supplementing with 100–150 μg of selenium per day for 5–6 weeks notably improved mood scores (Sajjadi et al. 2022).

20.3.1.2 Macronutrients

Changes in one macronutrient's intake correspond to changes in others, making it impossible to modify one alone. Research suggests a link between depression and overall macronutrient consumption. Interestingly, diets with varied macronutrient compositions don't impact depressive symptoms, but weight loss-oriented diets tend to alleviate these symptoms, regardless of macronutrient content (El Ghoch et al. 2016).

Carbohydrate

There is no direct association between overall carbohydrate intake and depression. Specifically, while higher consumption of lactose and fiber correlates with reduced depression risk, no such correlation is found between glucose, sucrose, fructose, or starch intake and the onset of depression (Gangwisch et al. 2015). Moreover, the macronutrient distribution in a low-calorie diet has minimal impact on depressive symptoms in non-depressed individuals (Patsalos et al. 2021). On the other hand, high-glycemic-load diets exhibit notable effects such as mood swings, heightened fatigue, and increased feelings of depression compared to low-glycemic diets. Prospective cohort studies indicate a link between an elevated risk of depression and increased consumption of added sugars from sugar-sweetened beverages, refined carbohydrates, and sugary meals. This heightened consumption of added sugars elevates the risk of incident depression, while total sugar or carbohydrate intake does not show a similar association, as observed in the Women's Health Initiative cohort (Knüppel et al. 2017). Additionally, higher fiber intake in this cohort is associated with a decreased risk of developing depression. Importantly, the quality of carbohydrates appears to have a more pronounced impact on depression risk than the quantity consumed.

Published studies have utilized the glycemic index and carbohydrate quality index to measure the intake of higher-quality carbohydrates. However, it is worth noting that the glycemic response to carbohydrate consumption cannot be reliably predicted solely based on the glycemic index (Rahimlou et al. 2018; Salari-Moghaddam et al. 2019).

Current dietary guidelines often advocate for choosing whole-grain carbohydrates over processed ones. Some studies have linked exercise to a reduction in depressive symptoms, hinting that exercise might counterbalance potential impacts of diet in certain cases (Dijksterhuis et al. 2022).

Fats

Recent research has significantly expanded our understanding of the link between fatty acids and mood disorders. Multiple studies have shown the positive impact of omega-3 polyunsaturated fatty acid supplementation on depressive symptoms. These benefits were particularly evident in formulations rich in EPA, with recommendations suggesting using these formulations at doses around 1 g per day for optimal results in treating unipolar depression. It is important to note that various fatty acids have distinct physiological effects (Advisory 2017).

The human body lacks the ability to internally produce the essential long-chain polyunsaturated fatty acids (PUFAs) families: *n*-3 and *n*-6 fatty acids (Van Dael 2021). As a result, these fatty acids or their precursor molecules must be included in diets. Both parent fatty acids can undergo desaturation and elongation processes, leading to the creation of longer chain PUFAs. Notably, the conversion of α-linolenic acid to *n*-3 PUFA is inefficient in humans, increasing reliance on seafood to fulfill *n*-3 PUFA needs. Furthermore, higher consumption of omega-6 PUFA, specifically linoleic acid, has been linked to an increased risk of depression. Although the impact of *n*-3 PUFAs on mental health is quite multifaceted, EPA and DHA, among these PUFAs, are highly concentrated in brain and particularly crucial for mental well-being (Dighriri et al. 2022).

PUFAs serve as fundamental building blocks in the phospholipid membranes of all body tissues, playing a vital role in the brain's neuronal membranes. Their presence significantly influences membrane properties, affecting receptor function, neurotransmitter uptake, and signal transmission. DHA, being the predominant *n*-3 PUFA in the brain, enhances serotonin receptor sensitivity by augmenting membrane flexibility. Furthermore, *n*-3 PUFAs act as precursors to specific prostaglandins and leukotrienes, playing roles in vasodilation, platelet aggregation inhibition, and inflammation reduction. These functions collectively contribute to their impact on mental health and well-being (Deane et al. 2021).

Proteins

The National Health and Nutrition Examination Follow-Up Study highlighted a potential link between higher protein intake and a reduced risk of severe depression. However, in women, while overall protein intake didn't correlate with mood, a higher proportion of energy from protein was associated with increased depression severity (Oh, Yun et al. 2020). Similarly, a study among male Japanese workers found no direct association between protein, fat, and carbohydrate intake and depressive symptoms, but plant-based protein intake showed a potential link to lower odds of depression (Nanri et al. 2014). Additionally, in a meta-analysis study, increased consumption of fish and shellfish was tied to a decrease in depressive symptoms (Li et al. 2016). Interestingly, depressive symptoms were also linked to reduced intake of red or processed meat and increased dairy consumption (Mofrad et al. 2021). For mood enhancement, foods rich in tryptophan, a serotonin precursor, along with a balanced profile of monoamine reuptake and MAO-A inhibition, might be effective. Tryptophan, an essential amino acid in mammals, is exclusively obtained from food sources and can potentially contribute to mood regulation (Hulsken et al. 2013).

20.4 Anxiety Disorders

One of the most reported mental illnesses is anxiety disorder, which is marked by symptoms such as worry, behavioral and social nervousness, unplanned or prompted panic attacks, dread of the future, and avoidance actions. According to the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), common anxiety disorders observed in primary healthcare include generalized anxiety disorder (6.2% lifelong prevalence), social anxiety disorder (13% lifelong prevalence), and panic disorder (5.2% lifelong prevalence), along with agoraphobia. Palpitations, dyspnea, and vertigo are examples of physical symptoms linked to anxiety (Szuhany and Simon 2022). Anxiety was previously thought as a healthy reaction to stressful circumstances, but when it interferes with regular physical, psychological, or social functioning, it is regarded as a pathologic illness (Rakhman et al. 2022). Anxiety is a common condition that is linked to significant disability, leading to a significant medical and financial cost. There is strong evidence that anxiety disorder is fairly widespread (25% of population) and is more common in women (8.7%), young adults (9.1%), and people with chronic illnesses (70%) (Remes et al. 2016).

20.4.1 Drawbacks of Anxiolytic Drugs

Anxiety disorders can be treated with medication and psychotherapy. Pharmacological treatments showed a better response than psychological therapy in a meta-analysis encompassing 37,333 patients with anxiety disorders (Slee et al. 2019). First-line pharmacological therapies for anxiety disorders include SSRIs and serotonin-norepinephrine reuptake inhibitors. However, it is unavoidable that these synthetic medications could create a number of side effects, such as nausea, diarrhea, decreased appetite, restlessness, insomnia, somnolence, sexual dysfunction, and hyponatremia (Bandelow et al. 2023). Other problems that restrict the effectiveness of medication include: First of all, they were created as stand-alone remedies rather than as a component of an integrative strategy, thus they don't always function effectively when combined with other psychiatric strategies. For instance, by reducing the sensation of emotional arousal, benzodiazepines may reduce the effectiveness of those agents (Apolinário-Hagen et al. 2020). Antidepressants may also make it harder to access emotional states; in a recent survey, 60% of respondents said they felt emotionally numb (Read and Williams 2018). Second, a lot of people don't react well to medication; response rates to SSRIs have been estimated to be around 60 and 75% (Jakubovski et al. 2019). Third, stopping medication might result in undesirable side effects and withdrawal symptoms that need to be carefully managed. Furthermore, pharmaceutical therapies have additional variety of unacceptable side effects, such as detrimental effects on hunger, sleep, and sexual functioning (Bandelow 2020).

Concurrently, due to safety concerns and adverse effects associated with conventional pharmacotherapy, alternative psychopharmacology research has gained attention after decades of reliance on prescription, mostly synthetic anxiolytics. Furthermore, people are encouraged to look for fresh natural cures instead of the present pharmaceutical drugs due to a spike in health knowledge, comprehensive medical views, and active healthcare engagement (Trkulja and Barić 2020).

20.4.2 Nutritional Management of Anxiety

In comparison with pharmacological treatment, research to date suggests that using nutritional and herbal remedies instead of pharmaceuticals may have some significant advantages over current treatments. While most medications have just one active ingredient to produce therapeutic effects, nutritional compounds and plant extracts usually have many different psychoactive ingredients (Gonçalves et al. 2021). This could seem like a challenge to producers that want to offer a highly standardized treatment and attempt to separate individual active ingredients. Any attempt to simplify the complicated arrangement of chemicals would, however, ignore the fact that a vital component of their therapeutic benefit is the synergistic and polyvalent interaction between the constituents (Butnariu and Butu 2021).

20.4.2.1 Nutrients of Phytomedicine Source

In the past few decades, the usage of phytomedicines for alleviating anxiety has significantly increased. A review of preclinical and clinical research found that a number of phytomedicines, including chamomile, ginkgo biloba, passionflower, kava, and Valerian, modulate the GABA signaling to produce anxiolytic effects comparable to those of modern synthetic medications (Zhang et al. 2022). In addition to their good safety and wider tolerability profiles, several meta-analyses have shown the well-documented effects of Saffron and Silexan for the reduction of anxiety when compared with a placebo treatment. According to a systematic evaluation of 100 publications containing 38 botanicals, the therapeutic benefits of silexan, saffron, and passionflower were on par with those of common anxiolytics and antidepressants (Marx et al. 2019; Donelli et al. 2019). According to those papers, medicinal herbs have better risk–benefit profiles than the anxiolytics used today, making them potentially useful for supplemental or alternative anxiety treatments.

20.4.2.2 Nutrients Affecting Microbiota

In addressing the possible anxiolytics of dietary therapies, a recent research tackled the underlying metabolic diseases related to anxiety disorders, based on that anxiety is linked to microbiome dysbiosis, and the composition of the microbes in the gut can control mental health (Norwitz and Naidoo 2021). The gut is home to trillions of bacteria that can affect mental health through hormonal and inflammatory regulation, communication with the brain, and other processes. The microbiota affects the amygdala, a brain region that controls the danger response and becomes overactive in anxiety disorders (Navarro-Tapia et al. 2021). Anxiety can be influenced by gut peptides that bind to receptors located in amygdala, such as neuropeptide Y and glucagon-like peptide 1. In addition, certain gut bacteria create short chain fatty acids, which control the release of gut peptides (Wei et al. 2020). Indeed, people who experience anxiety have lower populations of these species. Through emphasizing the roles of the microbiota, particular nutrients were found to modulate the microbiome and the microbiome-brain axis.

In these premises, the microbiota, mental health, and cognitive function are all enhanced by omega-3 fatty acids, particularly EPA and DHA, which also have anti-inflammatory qualities (Fu et al. 2021). Mice that are genetically modified to biosynthesize omega-3 fatty acids have microbiomes that are healthier, with less inflammation, and fewer chronic diseases (Kaliannan et al. 2019). Diets rich in omega-3 fatty acids have been demonstrated to restore normal dopamine levels and lessen anxiety-like behaviors in rats with inflammation-induced anxiety (Fig. 20.2) (Fu et al. 2021). Further, Omega-3 supplements have been demonstrated to reduce anxiety levels in people, while lower levels of EPA and DHA are linked to grater anxiety severity. Besides, research has indicated that supplements with lower amounts of DHA and doses less than 2 g daily are less beneficial in mitigating anxiety (Su et al. 2018).

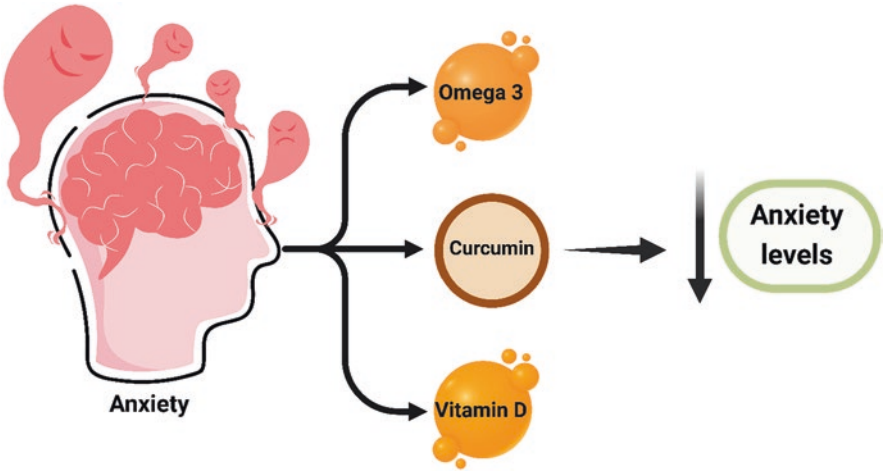

Fig. 20.2 Different nutritional factors alleviating anxiety

20.4.2.3 Curcumin

Another nutritional supplement with numerous studies conducted on its possible advantages is turmeric, particularly its active ingredient curcumin, known for its brain health enhancing properities, like in depression, anxiety, Parkinson's disease, and Alzheimer's disease. Curcumin works through a variety of ways, such as enhancing the microbiome of the gut, decreasing inflammation, controlling hormone and neurotransmitter levels, and affecting histone deacetylases and microRNAs (Bhat et al. 2019). Curcumin efficiently reduces anxiety-like behaviors and raises hormone and neurotransmitter levels in rodents, according to preclinical experiments. It has been discovered that in mice devoid of sleep, curcumin prevents anxiety. The inhibition of nitric oxide and oxidative damage was the mechanism behind curcumin's protective action. In a different study, rats exposed to lead demonstrated the anti-anxiety effects of curcumin, which may involve a modification of monoaminergic neurotransmission. Additionally, after administering curcumin to mice, there was a decrease in anxiolitic behavior and a rise in the brain's production of docosahexaenoic acid, an agent that is closely associated to anxiety. Furthermore, The putative corrector action of curcumin, which involves the removal or detoxification of chemicals generated by sulfites in the nerve tissue, may account for its effectiveness in treating sulfite-induced anxiety (Noorafshan et al. 2017). Supplementing with curcumin has been shown in numerous randomized controlled trials to alleviate anxiety in people, especially in those with diabetes and obesity (Fig. 20.2) (Asadi et al. 2020; Esmaily et al. 2015). The curcumin literature does, however, have certain drawbacks, such as problems with its chemical stability, variations in the purity and formulations of supplements, and low absorption (Zhang et al. 2019).

20.4.2.4 Vitamin D

Due to high latitudes and contemporary lifestyles, endogenous vitamin D production is often inadequate, which impedes vitamin D supplementation through diet (Bouillon et al. 2022). Vitamin D has a major impact on brain inflammation, neurotransmitter levels, and calcium homeostasis. Reduced levels of vitamin D have been associated with mental health conditions such as anxiety, depression, and SCZ (Bivona et al. 2019). It was confirmed that vitamin D protects dopaminergic neurons against neuroinflammation and oxidative stress (Renteria et al. 2024). Patients who are suffering anxiety might consider vitamin D supplementation since it has been demonstrated to be effective in alleviating anxiety symptoms in individuals who have declined levels of this vitamin (Fig. 20.2) (Sharifan et al. 2023).

20.4.2.5 Ketogenic-Rich Diet

In the same aspect, ketogenic diets have been used to treat epilepsy and neurological disorders and are becoming more popular as a metabolic therapy for chronic metabolic problems (Zhu et al. 2022). According to recent research, ketogenic diets could assist in managing a number of mental health conditions, such as depression, bipolar disorder, Attention deficit hyperactivity disorder, and SCZ. Ketogenic diets can improve glucose metabolism, neurotransmitter balance, oxidative stress, and inflammation, thereby addressing the biopathological bases of neurological diseases and mental illnesses (Danan et al. 2022). Exogenous ketone supplementation and ketosis cause anti-anxiety benefits and brain changes that lessen anxiety, according to preclinical research conducted on rats (Ari et al. 2017). Although there is a lack of specific clinical studies evaluating the effectiveness of ketogenic diets for anxiety, they have been considered to be a potentially beneficial therapeutic option in the future for mental health issues (Dietch et al. 2023).

20.4.2.6 Gluten

On the other hand, Gluten was found to induce inflammation by increasing gut permeability and allowing immune-stimulating compounds to leak into the bloodstream (Cenni et al. 2023). Zonulin protein, which is overexpressed in celiac disease, has been linked to mental illnesses such as social phobia, panic attacks, and other forms of anxiety (Asbjornsdottir et al. 2020; Stevens et al. 2018). While a gluten-free diet has only been shown to decrease anxiety in celiac patients, it may still be beneficial for treating anxiety due to the link between gluten, “leaky gut,” and mental illness (Caio et al. 2020).

20.4.2.7 Mediterranean Diet

In a clinical study focused on the relation between The Mediterranean Diet Score and anxiety, a correlation with non-refined grains, vegetables, and alcohol use was found. The study showed that adherence to the Mediterranean diet, especially greater consumption of non-refined grains and vegetables, may help prevent or lessen anxiety (Gibson-Smith et al. 2020).

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Chapter 21
The Western Diet Puzzle: Connecting Metabolic Dysfunction to Cognitive and Neurological Consequences

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Abstract There has been a significant rise in the consumption of Western diet (WD), which are diets composed of high levels of processed sugar and saturated fat. This unhealthy eating habit has been linked to the development of several chronic diseases, such as obesity, diabetes mellitus, metabolic syndrome, and cardiovascular diseases. Although the effect of WD on metabolic and cardiovascular impairment has received significant attention, how it influences brain function, both in normal and pathologic states is just beginning to gain recent interest. WD has been linked to the alteration of cognitive and neurological function, which is a phenotype that is observed in several neurological disorders such as Alzheimer's disease, Parkinson's disease, and traumatic brain injury. The underlying mechanism through which WD induces this effect involves the alteration of cellular homeostasis in the brain microenvironment, which triggers neuroinflammation and the activation of glial cells. Additionally, energy metabolism within the brain is disrupted, leading to the uncoupling of the mitochondria, increased release of ROS, and oxidative stress. Since synaptic plasticity is an energy-intensive process, the distortion of metabolism significantly impacts synaptic plasticity, which potentially leads to altered learning and memory processes and cognitive dysfunction. Also, WD alters the expression of key synaptic proteins that are involved in cognition. This book chapter highlights the cellular and molecular mechanism, through which WD impacts brain function. Also, it details how WD influences the pathologies of several neurological disorders and can lead to worsened functional outcomes.

Keywords Western diet · High-fat diet · Ketogenic diets · Neurological disorders · Neuroinflammation

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21.1 Introduction

Over the last decades, there has been a significant rise in the rate of metabolic syndrome-induced obesity in different countries. It has been predicted that over 50% of Americans will be overweight by 2030 (Finkelstein et al. 2012). This is primarily caused by the gradual shift towards consuming a Western diet (WD) (diet rich in sugar and saturated fat), coupled with an increase in a sedentary lifestyle. Specifically, the consumption of a high-fat diet has been linked to the development of metabolic syndrome, which is a metabolic disorder that usually arises due to at least three of these conditions: hypertension, diabetes, obesity, and hypertriglyceridemia (Drake et al. 2018). This further triggers inflammatory and oxidative alterations, thereby predisposing to major health conditions, among which include diabetes mellitus, neurological and neurodegenerative disorders, and cardiovascular dysfunction (Clemente-Suárez et al. 2023). There has been increasing interest in the role that WD plays in brain health and function. This is due to the significant rise in the consumption of the WD diet, which has been worsened due to the lockdowns caused by the COVID-19 pandemic (Sidor and Rzymski 2020). One of the significant effects of WD consumption is obesity, which has been reported as a significant risk factor for cognitive decline (Tsan et al. 2021). In this chapter, we discuss how WD affects brain function and how it can predispose to neurodegeneration.

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21.2 Brain Metabolism

The brain is an energy-intensive organ, that adopts a unique metabolic pattern, primarily utilizing glucose as the main source of energy, while retaining the ability to also get energy from ketone bodies (KBs). Crosstalk between neurons and glial cells mediates the highly controlled process of energy metabolism in the brain. Energy balance in a healthy brain is ensured by this well-regulated cellular interaction, which is essential for appropriate brain function (Dienel 2014). During neurological defects, cellular homeostasis within the brain is disturbed leading to dysfunctional brain energy metabolism. For example, a rapid distortion of brain function could arise from any metabolic imbalance impacting glucose availability without a compensatory ketogenic utilization. It is interesting to note that behavioral and cognitive disorders have been directly linked to a metabolic imbalance within the brain (Watts et al. 2018; Morella et al. 2022).

21.2.1 Glucose Metabolism Within the Brain

Despite the brain contributing only 2% of the total body weight, it is the highest glucose-consuming organ in the body, utilizing about 20% of the total body glucose. Despite this huge glucose demand by the brain, it cannot store glucose, and hence, needs a continuous supply of it. With the brain being composed of over 100 billion neurons and many more glial cells, it is estimated that the brain consumes about 420 kcal of energy per day (El Bacha et al. 2010). Just 10–15% of this energy is needed to maintain the resting membrane potential; the majority is used for the manufacture of neurotransmitters and the upkeep of ionic gradients, which are necessary for the transmission of nerve impulses. Hence, any disorder that interrupts glucose supply to the brain can predispose to severe pathologies (Ritter 2017). Glucose is metabolized within the brain in a concerted effort between astrocytes and neurons, where astrocytes metabolize glucose to lactate, which it can then release to neurons via monocarboxylate transporters (MCTs). Additionally, the end feet of astrocytes are strategically positioned beside neurons to mediate neuro-metabolic coupling. When glutamate accumulates at the synaptic space, the excessive glutamates are taken up by astrocytes through the Na^+-dependent transporters (EAAT-1 and EAAT-2). This leads to increased intracellular Na^+, activation of the Na^+/K^+ ATPase, and ATP consumption (Habashy et al. 2022). Consequentially, the increased ATP usage stimulates increased glucose uptake by astrocytes, which it then converts to lactate and releases to neurons. Once inside neurons, lactate is transformed into pyruvate, which can be easily metabolized in the mitochondria by oxidative phosphorylation of the tricarboxylic acid cycle (TCA) (Beard et al. 2022; Mergenthaler et al. 2013). In this situation, astrocytes support neurometabolic coupling as well as the restoration of extracellular glutamate concentrations, thereby preventing excitotoxicity (Habashy et al. 2022). Also, despite the TCA cycle playing a significant role

in brain energy metabolism, it results in the generation of reactive oxygen species (ROS) (Murphy 2009). Interestingly, neurons hugely depend on antioxidants derived from astrocytes to counter the ROS. For instance, ascorbic acid is a major antioxidant that is generated by astrocytes in response to glutamate stimulation and is absorbed by neurons. In neurons, ascorbic acid alters the metabolic substrates of neuronal cells by inhibiting the metabolism of glucose and boosting the intake of lactate (Castro et al. 2009). Hence, neuron-glia communication is necessary for maintaining the brain's energy homeostasis. However, under circumstances such as prolonged starvation or diabetes, this balance is typically disturbed, causing a metabolic shift from glucose to KBs as the energy substrate (López-Ojeda and Hurley 2023).

21.2.2 Ketone Body Metabolism Within the Brain

KBs make up between 5% and 20% of the body's overall energy consumption and are an essential source of energy for the brain (Abdul Kadir et al. 2020; Dhillon and Gupta 2023). During periods of sustained glucose deprivation or starvation, fatty acids are converted into KB and released into the general circulation, where they are absorbed via the bloodstream and delivered to different organs to serve as an alternative energy source. KB entrance into the brain is carrier-dependent, and mainly trafficked by MCTs. Upon entrance into the brain, they can be converted back to acetyl CoA, and fed into the TCA cycle for oxidative metabolism (Habashy et al. 2022). In several disease conditions like diabetes mellitus, the cells are deprived of glucose, which leads to a switch in brain energy metabolism, favoring KB utilization (Veneti et al. 2023). KB uptake in the brain depends on the expression of MCTs in each cell. For instance, while MCT1, an isoform of MCT is expressed in endothelial cells and astrocytes at the neurovascular unit and facilitates quick uptake of KB from the blood, MCT2 is almost exclusively expressed in neurons. This means that most of the cells in the brain can take up and metabolize KBs (Habashy et al. 2022).

21.3 Western Diet

The popular phrase "we are what we eat" denotes that a person's diet can significantly impact the quality of their health. A significant portion of the diet that is heavily consumed by a huge population is made up of fats. Dietary fats are important for organ and systemic activities since they are a primary source of energy for many organs. On the other hand, the ratio of fat to carbohydrates in a diet can impact how healthy a person is. Hence, fat-containing diets are generally classified into two categories: ketogenic diets which are high-fat low carbohydrate diets, and WD which are high fat-high carbohydrate diets (Bakkar et al. 2023). While ketogenic diets have been reported to improve cognitive abilities and confer positive health

benefits to the brain, WD leads to cardiovascular and neurological dysfunction and has been shown to aggravate the effect of several neurological and neurodegenerative disorders (Habashy et al. 2022).

21.3.1 Metabolic Syndrome: Linking WD-Induced Systemic Alterations to Chronic Diseases

WD could include several sugary drinks, fast foods, and foods obtained from convenience stores. Due to the calorie density of these diets, they have a high glycemic index, and can significantly increase blood sugar levels, thereby predisposing the consumers to diabetes (Kopp 2019). Furthermore, cardiovascular, cerebrovascular impairment, and obesity have been linked to increased WD consumption (Clemente-Suárez et al. 2023). Obesity poses a significant threat to health and can predispose to several life-threatening conditions such as cardiovascular impairment. It is currently one of the leading causes of death worldwide, affecting over 1.9 billion adults as of 2016 (Rakhra et al. 2020). In the USA alone, an estimated 42.4% of the population was reported to be overweight as of 2017, and this has led to an epidemic of several other chronic disorders such as diabetes, cardiovascular diseases, and neurodegenerative disorders (Kopp 2019). One of the canonical consequences resulting from obesity is insulin resistance. Insulin plays a significant role in regulating the uptake and utilization of glucose by cells; hence, abnormal levels of insulin can signify metabolic dysfunction (Roberts et al. 2013). Interestingly, WD has been shown to induce insulin resistance, thereby resulting in elevated insulin levels in the blood, which can potentially impair glucose uptake, disrupt energy metabolism, and predispose to diabetes mellitus (Kopp 2019). Also, due to hyperinsulinemia, metabolic dysregulation ensues, leading to increased fat storage, while lipolysis is downregulated. This ultimately leads to increased fat mass in adiposities, thereby resulting in obesity (Mehran et al. 2012; Ludwig and Ebbeling 2018). Several studies have reported a significant weight gain in individuals with hyperinsulinemia (Kopp 2019; Sigal et al. 1997; Chen et al. 2015). Another consequence of WD-induced pathologies is cardiovascular impairment, mainly driven by vascular endothelial dysfunction. This arises due to the disruption of endothelial-dependent dilation of vascular smooth muscle cells and has been reported in several diseases such as diabetes mellitus and atherosclerosis (Elrashidy et al. 2019). Vasodilation is primarily regulated by the activity of the endothelial nitric oxide synthase (eNOS), which converts L-arginine to nitric oxide (NO), which then acts as a vasodilator (Förstermann and Sessa 2012). Hence, pathologies that impact eNOS expression or bioavailability could have a deteriorating effect on vasodilation and cardiovascular function. WD-induced elevation of ROS has been reported to uncouple eNOS, thereby resulting in the disruption of endothelial function (Elrashidy et al. 2019). Consequentially, disruption of vasodilation leads to elevation of blood pressure and heart rate, which can predispose to hypertension and other cardiovascular abnormalities. Additionally,

superoxide radicals can interact with NO to form peroxynitrite, which sequesters NO, thereby reducing its bioavailability (Peluffo et al. 2009). In addition to hyperinsulinemia, WD-induced production, and release of ROS trigger inflammatory responses in tissues. Given that inflammatory markers are shown to rise in the serum following WD consumption, systemic inflammation is likely one of the primary mechanisms by which WD produces its wide range of effects (Lopez-Garcia et al. 2004). A sedentary lifestyle and the consumption of WD are associated with the emergence of "metaflammation", a kind of chronic metabolic inflammation that is linked to the pathophysiology of several non-communicable diseases (Christ et al. 2019). Concertedly, inflammation, the disruption of energy metabolism together with the oxidative environment, leads to the uncoupling of the mitochondria, thereby resulting in aggravated effects on energy metabolism within the cell. Uncouple proteins (UCPs), which play a significant role in the uncoupling of mitochondrial oxidative metabolism, are known to be induced by high fat-containing WD (Bakkar et al. 2023).

21.3.2 Western Diet and the Brain: From Pathology to Neurological Impairment

Although the brain is well shielded by the BBB which restricts the movement of inflammatory mediators into the brain, studies have shown that several factors, including those not found within the brain, can trigger inflammatory responses in the brain and impair neurological and cognitive function (Boyd et al. 2022; Oza et al. 2023; Langley et al. 2022). One of these factors is the choice of diet. Particularly, WD has been reported to exert negative effects on the brain, that are similar to the impairments observed in several neurological disorders (Graham et al. 2016).

21.3.3 WD Impairs Cognitive and Neurological Function

One of the most essential functions of the brain is its ability to regulate nerve impulses. The concept of synaptic plasticity, which involves neurotransmission between two neurons is a fundamental process that underlies learning and memory processes. Hence, plasticity is impaired in several neurological and neurodegenerative diseases and underscores the cognitive decline observed in these disorders (Duclos et al. 2018; Lepeta et al. 2016). Likewise, WD has been shown to induce notable cognitive and behavioral impairment in experimental animals, of which the expression of synaptic proteins that regulate plasticity is reduced in these animals (González Olmo et al. 2023; Liu et al. 2017). For instance, WD consumption in pregnant rats has been reported to alter cognition up to the third-generation offspring of these rats (Lin et al. 2021). Interestingly, it has been demonstrated that

WD reduced the expression of synapsin I, CREB, and BDNF (Wu et al. 2004; Cavaliere et al. 2019). BDNF is a neurotrophic factor, which when released, binds to its post-synaptic receptor (TrkB), to initiate a signaling process that enhances neuroplasticity. Additionally, Protein kinase B (Akt) is involved in the pathway that activates CREB, which is phosphorylated by CAMK-II to propagate plasticity-related signaling. On the other hand, the Insulin Growth Factor-I receptor (IGF-IR) is upstream of Akt. Thus, changes in brain insulin sensitivity, such as those associated with WD, may impact CREB activation and neuroplasticity (Gómez-Pinilla 2008; Leinninger et al. 2004; Yan et al. 2016). Interestingly, neuronal synapses are enriched with insulin receptors, reaffirming their involvement in neuroplasticity (Penna et al. 2020; Spinelli et al. 2020).

WD also poses some indirect effects on synaptic plasticity. For instance, WD-induced obesity causes the activation of microglia and astrocytes, which leads to neuroinflammation and the release of inflammatory mediators within the brain. The obesity-induced neuroinflammatory response has been shown to affect the expression of synaptic genes. This includes genes that are involved in neurotransmitter release such as SNAP-25, ultimately leading to a reduction of synapse density and impairing synaptic plasticity (Penna et al. 2020; Wang et al. 2020; Valcarcel-Ares et al. 2019).

21.3.4 WD Alters Energy Metabolism Within the Brain

Beyond its role it is modulating energy metabolism in the body, WD has been shown to alter brain metabolism. For instance, WD impairs mitochondria oxidative metabolism in the brain cortex. This was associated with increased neuroinflammation and oxidative stress (Habashy et al. 2022; Langley et al. 2020). Brain energy metabolism is essential for proper brain function. Since synaptic plasticity, which underlies learning and memory is energy intensive (Li and van Rossum 2020), hence, alteration in brain energy homeostasis can impact cognitive function. Interestingly, the altered mitochondria oxidative metabolism was also observed in synaptosome fractions, signifying metabolic impairment even at the synapses. This was associated with reduced expression of the neurotrophic factor BDNF and impaired synaptic plasticity (Cavaliere et al. 2019).

In another study, WD resulted in a significant body weight increase and the development of insulin resistance. This in turn led to an impairment of cellular glucose uptake and utilization, thereby disrupting energy homeostasis (Liu et al. 2017). Consequently, glycolytic and acetate metabolism in both neurons and astrocytes were distorted, signify, and have brain-wide effect on energy metabolism. The alteration of brain energy homeostasis in these was accompanied by a significant reduction in the excitatory postsynaptic potential (EPSP), thereby linking WD-induced alteration of brain energetics to synaptic impairment (Liu et al. 2017). Additionally, several neurochemicals that are involved in brain intermediary metabolism are altered in mice fed with WD (Raider et al. 2016). Alteration of brain energy

homeostasis is a marker of brain aging and several neurodegenerative diseases (Błaszczyk 2020), which has also been observed in neurological insults such as traumatic brain injury (TBI) (Xu et al. 2021). Therefore, WD-induced impairment of brain bioenergetics could predispose the brain to severe neurological impairment.

21.3.5 Neuroinflammation and Oxidative Stress

Microglia are the primary immune cells in the brain and play a significant role in surveying the brain and responding to any form of inflammatory mediators. Although the activation of microglia is a protective mechanism initiated by the brain against any inflammatory effect, when they are chronically activated, they polarize from the neuroprotective anti-inflammatory form to the pro-inflammatory form, which potentially causes more damage to the brain (Haidar et al. 2022). In this state, the BBB could become distorted, leading to an influx of more pro-inflammatory mediators into the brain. WD has been reported to induce both system and brain-specific inflammatory responses. For instance, serum levels of the pro-inflammatory TNF-α and IL-1β were significantly increased following WD in mice (Cavaliere et al. 2019). However, the elevated levels of these inflammatory mediators were not only observed in the serum, but also in the brain cortex, and synaptosome fractions, indicating heightened inflammation even at the synapses (Cavaliere et al. 2019). In a different study, just 2 days of WD feeding led to a significant increase in the expression of TNF-α, IL-1β, and IL-6. This early release of inflammatory mediators was accompanied by a significant distortion of BBB integrity, shown by increased permeabilization of sodium fluorescein into the brain (de Paula et al. 2021). Consequently, these mice displayed depression-like behaviors and altered memory patterns. Likewise, WD has been reported to cause elevated release of ROS in the brain, while significantly impairing antioxidant defense systems (Ibeh et al. 2023). Mice fed with WD had increased cortical and synaptosomal malondialdehyde (MDA) levels, which is a product of oxidative stress-induced lipid peroxidation (Cavaliere et al. 2019). The increased levels of MDA were parallelled by a reduction in the ratio of reduced-to-oxidized glutathione (GSH/GSSG). In a different study, WD resulted in a decline in the level of hippocampal Nrf2, which is a transcription factor that regulates the expression of several antioxidant proteins. Interestingly, the reduced expression of Nrf2 was followed by cognitive impairment (Morrison et al. 2010).

21.3.6 WD in Neurological Disorders

21.3.6.1 WD and TBI

TBI is a major public health concern and represents one of the leading causes of mortality and morbidity across all ages. It is a brain disorder that has an impact on the head, which can disrupt normal brain function and affect behavior (Capizzi et al. 2020). A single brain injury event can affect a variety of behavioral, cognitive, and molecular functions in the body, hence, the consequences resulting from TBI are complex and unique to everyone. Although TBI affects people in all populations, those involved in contact sports and the armed forces are particularly vulnerable to it (National Academies of Sciences, Engineering, and Medicine et al. 2022; Peskind et al. 2013).

There are about 50 million TBI cases worldwide, with the USA reporting over 2.5 million TBI-related hospitalizations. Beyond the strain it possesses on the health care system, TBI also poses a major economic burden to countries. For instance, in the USA, approximately 77 billion USD is spent on TBI every year (National Academies of Sciences, Engineering, and Medicine et al. 2022). Injury arising from TBI can be a primary injury, which is the initial injury at the point of impact. However, the primary injury can progress into several cellular and molecular alterations thereby leading to secondary injuries that result in oxidative stress, neuroinflammation, excitotoxicity, altered cell metabolism, and apoptosis (McKee and Daneshvar 2015).

WD has been shown to influence the outcome of TBI and aggravate the functional alterations induced by the secondary injury. Our group has shown that WD exacerbates TBI-induced functional impairments. C57Bl6 mice were fed on HFD for 1 month, before being subjected to an open head control cortical impact (CCI) injury. After the injury, the mice were fed for an additional 1 month (Ibeh et al. 2023). Neuroinflammation was marked by increased activation of microglia and astrocytes, which was accompanied by elevated ROS levels, as well as the downregulation of the brain antioxidant defense system. Additionally, WD feeding slowed down the post-TBI recovery process by downregulating cell proliferation in the ipsilateral brain region. This led to a significantly high lesion volume of the WD-fed TBI mice after 30 days post-TBI (Ibeh et al. 2023). The aggravated function impairment observed following WD resulted in significant cognitive, neurological, and behavioral derangements (Ibeh et al. 2023; Hoane et al. 2011; Shaito et al. 2020). In a different study, chronic WD feeding resulted in worsened neuroinflammation and the exacerbation of anxiety-like behaviors (Sherman et al. 2016). The functional impairments observed in TBI victims can range from cognitive impairment due to altered synaptic function, to neurological and behavioral derangements. Wu et al. reported that rats fed WD before and after TBI demonstrated significantly worsened learning and memory impairments. Additionally, these rats have reduced levels of BDNF, CREB, and synapsin (Wu et al. 2003) A different study found that anxiety-like behavior following a TBI is related to BDNF

signaling. In particular, decreased expression of the anxiolytic substrate neuropeptide Y1 (NPY1) and its cognate receptor (NPY1R) was linked to decreased expression of BDNF and CREB, suggesting a link between WD and an increased risk of post-traumatic stress disorder. Interestingly, elevated levels of IL-1α expression in the frontal cortex of rats administered WD suggested that these alterations were caused by worsened neuroinflammation (Bakkar et al. 2023; Tyagi et al. 2013). Beyond aggravating post-TBI effects, WD has been shown to cause telomere shortening, and increased phosphorylation of Tau proteins, which could propagate post-TBI effects into neurodegeneration (Ibeh et al. 2023; Mychasiuk et al. 2015).

21.3.6.2 WD and Parkinson's Disease

PD is a neurodegenerative disease that is characterized by neuronal cell death in the substantia nigra, primarily dopaminergic neurons. It is important to treat PD promptly as it can worsen quickly and lead to incapacitating side effects (Habashy et al. 2022). Speech and gait abnormalities are some of the most common characteristics of problems faced by PD patients. Although there are several treatments available to address PD symptoms and slow down the disease's progression, L-dopa is still the medication that is most commonly used (Habashy et al. 2022). However, L-dopa only partially resolved PD and its prolonged use could lead to further complications.

There has been an increased interest in the role that an unhealthy diet plays in PD. It has been reported that diets enriched with saturated fat and processed sugar are associated with an elevated risk for the development of PD (Zapała et al. 2022). Additionally, consumption of unhealthy WD has also been associated with faster progression of PD. It is interesting to note that WD alters the microbiome, favoring a microbial diversity that is comparable to that of PD patients and is thought to have a role in the neuroinflammation and pathogenesis of the illness (Habashy et al. 2022).

21.3.6.3 WD and Alzheimer's Disease (AD)

AD is a neurodegenerative disease that poses a significant threat to life. It has a huge global burden. As of 2015, an estimated 47 million persons live with AD, of which this number is projected to increase to 152 million by 2050 (Więckowska-Gacek et al. 2021). The phenotype of AD starts to manifest with mild cognitive impairment and memory loss, which then progresses to changes in behavior. It is the leading cause of dementia worldwide. Apolipoprotein E-4 (APO E), which is a well-known genetic risk factor for AD, is a lipoprotein that is involved in the transport of lipids and cholesterol. Hence, it is not unexpected that dietary fat composition may have an impact on dementia risk. Additionally, obesity has been reported to significantly increase the risk of dementia even after three decades (Whitmer et al. 2008). In older people, the negative consequences of obesity on cognitive processes are much

more pronounced. Consumption of WD has been associated with increased AD markers (Hill et al. 2019).

WD-induced obesity leads to the inhibition of the pyruvate dehydrogenase complex and induces metabolic dysfunction (Choi et al. 2018). Interestingly, metabolic dysfunction plays a crucial role in the pathologies of Alzheimer's. The accumulation of amyloid beta in Alzheimer's has been reported to be preceded by mitochondria impairment, and dysfunctional mitochondria have been observed in several models of Alzheimer's diseases (Caspersen et al. 2005; Devi et al. 2006; Martins et al. 2017; Swerdlow et al. 2014). Additionally, WD has been shown to impair learning and memory, which are significant phenotypes observed in dementia (Davidson et al. 2015; Jahn 2013). Mice fed with WD have been shown to have reduced levels of synaptophysin, dopamine, serotonin, BDNF, and acetylcholine, which are proteins that are involved in synaptic plasticity. This led to the alteration of LTP in these mice (Więckowska-Gacek et al. 2021; Lizarbe et al. 2019; Jena et al. 2018; Liu et al. 2014). Also, oxidative stress caused by increased lipid peroxidation, elevated ROS levels, and the downregulation of antioxidant defense systems have been observed after WD. Interestingly, this correlates with significant cognitive impairment and could serve as a link through which WD exacerbates AD. WD has been linked to elevated phosphorylation of Tau protein and the development of amyloid plaques in the hippocampus. Additionally, WD was also associated with increased synthesis and cleavage of amyloid precursor peptide (APP) (Habashy et al. 2022; Więckowska-Gacek et al. 2021; Xu et al. 2017; Selvi et al. 2017; Ho et al. 2004).

21.4 Conclusion

The need to pay attention to the kind of diet we consume has become increasingly more significant since diet choices have now been shown to significantly impact the quality of life. While the tremendous rise in the consumption of WD has been linked to the development of several cardiovascular and metabolic disorders, the increased sedentary lifestyle, which was worsened due to the COVID-19 lockdowns has contributed to these sequelae. Much more important is how WD impacts brain health. It is now evident that WD alters brain function by influencing neuroinflammation, oxidative stress, and neuroplasticity. This makes it a significant risk factor for neurodegeneration and can impair the recovery of individuals with neurological disorders.

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Chapter 22
Nutritional Psychiatry: The Present State of the Evidence

Mohamed Baklola

Abstract Nutritional Psychiatry (NP) represents an innovative field at the intersection of nutrition and mental health, offering new insights into the prevention and treatment of psychiatric disorders through dietary modifications and nutrient supplementation. Amidst a global escalation in mental health issues and the limitations of traditional psychiatric medications, NP emerges as a vital complementary approach, focusing on diet quality as a modifiable risk factor for mental disorders. This chapter provides a comprehensive overview of NP, elucidating its theoretical foundations, the biological mechanisms linking diet to mental health (including inflammation, oxidative stress, neuroplasticity, and the gut–brain axis), and the current evidence base for dietary impacts on major psychiatric disorders such as depression, anxiety, schizophrenia, bipolar disorder, and ADHD. The ultimate goal is to pave the way for more effective, holistic, and personalized mental health care that addresses the dietary as well as psychological needs of individuals, underscoring the critical role of nutrition in mental well-being.

Keywords Nutritional Psychiatry · Nutrition and mental health · Psychiatric disorders · Dietary modifications · Nutrient supplementation · Personalized care

22.1 Introduction

Nutritional Psychiatry (NP) has emerged as a groundbreaking field that bridges nutrition and mental health, offering a novel approach to understanding and managing psychiatric disorders (Prince et al. 2007). This interdisciplinary field posits that dietary modifications and targeted nutrient supplementation can play a pivotal role in preventing and treating mental health issues (Whiteford et al. 2013). At a time when the development of new psychiatric medications is plateauing, the

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significance of Nutritional Psychiatry comes into sharper focus against the backdrop of the escalating global burden of mental disorders (Walsh 2011).

The incidence of mental illnesses, a leading cause of disability worldwide, underscores a pressing health, social, and economic challenge (Walsh 2011; Whiteford et al. 2013). Mental, neurological, and substance use disorders collectively contribute to significant losses, estimated at $8.5 trillion in global output (Chisholm et al. 2016). Traditional treatments, including pharmacotherapy and psychotherapy, address less than half of the disease burden (Casacalenda et al. 2002; Olfson et al. 2015). This shortfall highlights the urgent need for innovative approaches (Olfson et al. 2015). The increasing prevalence of mental disorders, despite broader access to conventional treatments, points to the influence of environmental factors, including diet, on mental health.

Nutritional Psychiatry posits diet quality as a critical, modifiable risk factor for mental disorders (Marx et al. 2017). Systematic reviews reveal a robust inverse correlation between healthy dietary patterns—rich in vegetables, fruits, whole grains, nuts, seeds, and fish—and the risk of depression and anxiety (Lai et al. 2014). Conversely, diets laden with processed, sugary, and high-fat foods are positively associated with these disorders (Lai et al. 2014). This connection extends to early life, suggesting that maternal nutrition and childhood diet significantly impact emotional and behavioral development.

The exploration of biological mechanisms underpinning the diet–mental health nexus has spotlighted the roles of inflammation, oxidative stress, and neuroplasticity, with the gut microbiome emerging as a central mediator (Marx et al. 2017). This understanding has spurred the investigation of dietary and nutraceutical interventions targeting these pathways in the management of both common and severe psychiatric conditions. Recent clinical trials exploring whole diet interventions for depression exemplify the potential of Nutritional Psychiatry to revolutionize treatment paradigms (Lai et al. 2014; Opie et al. 2015; Psaltopoulou et al. 2013).

This chapter aims to provide a comprehensive overview of Nutritional Psychiatry, elucidating its theoretical foundations, methodological approaches, and the current state of evidence regarding dietary impacts on major psychiatric disorders. It will delve into the conceptual framework that underlies the relationship between diet, brain function, and mental health, followed by a discussion on the methodological challenges inherent in Nutritional Psychiatry research. Finally, we will discuss the challenges and future directions for Nutritional Psychiatry, offering practical implications for clinicians and patients and advocating for further research to solidify the evidence base. This chapter aspires to underscore the transformative potential of nutritional interventions in complementing traditional psychiatric treatments, paving the way for a more holistic approach to mental health care.

22.2 The Conceptual Framework of Nutritional Psychiatry

The emerging field of Nutritional Psychiatry rests on the premise that diet significantly impacts mental health through various biological pathways (Marx et al. 2017). This interdisciplinary approach emphasizes the role of nutritional interventions in preventing and managing mental disorders, underscoring the intricate relationship between diet, brain function, and mental health (Sarris 2019). Here, we delve into the theoretical underpinnings of Nutritional Psychiatry and explore the primary pathways through which diet influences mental illness, highlighting the potential for dietary modulation to support mental health.

22.2.1 Theoretical Underpinnings

Nutritional Psychiatry integrates principles from nutrition, psychology, and neuroscience to investigate how dietary patterns affect brain health and behavior (Sarris 2019). It posits that specific nutrients and overall dietary patterns can influence the development and management of mental disorders (Marx et al. 2017; Sarris 2019). This framework is built upon the recognition of diet as a key modifiable risk factor for mental health, offering a complementary approach to traditional pharmacological and psychotherapeutic treatments (Adan et al. 2019).

22.2.2 Relationship Between Diet, Brain Function, and Mental Health

Diet influences brain function and mental health through several key pathways:

- Inflammation: Chronic low-grade inflammation, marked by elevated pro-inflammatory cytokines, is linked to mental disorders such as depression, schizophrenia, and bipolar disorder (Fernandes et al. 2016a, b). Lifestyle factors, including diet, play a crucial role in modulating inflammation. Observational and intervention studies show that diets rich in polyunsaturated fatty acids (PUFAs), fiber, fruits, and vegetables, like the Mediterranean diet, are associated with reduced inflammation markers (Estruch 2010; Schwingshackl and Hoffmann 2014; Watzl et al. 2005).
- Oxidative stress: Oxidative stress, resulting from an imbalance between free radicals and antioxidants, affects brain health and is implicated in mental illnesses (Moylan et al. 2014). Studies have found reduced antioxidant levels in individuals with schizophrenia and depression (Liu et al. 2015). Diets high in antioxidants, found in fruits and vegetables, can mitigate oxidative stress, suggesting a modulatory role of diet (Deledda et al. 2021).

- Brain plasticity: Neurogenesis, particularly in the hippocampus, is vital for cognitive functions and mood regulation (Zainuddin and Thuret 2012). Altered neurogenesis is implicated in mental illness. Dietary components, such as n-3 fatty acids, polyphenols, and vitamins, can influence neurogenesis (Fernandes et al. 2014; Kawakita et al. 2006; Wakabayashi et al. 2012). Emerging evidence points to the potential of diet to enhance brain-derived neurotrophic factor (BDNF) levels, supporting brain plasticity (Williams et al. 2008).
- Microbiota–gut–brain axis: The gastrointestinal microbiota influences mental health through various neurobiological pathways, including BDNF modulation, serotonin neurotransmission, immune function, and stress response (Fung et al. 2017). Alterations in gut microbiota composition are linked to mental disorders (Dinan and Cryan 2012). Dietary interventions can modulate gut microbiota, impacting mental health-related behaviors (Hooper et al. 2012; O'Mahony et al. 2015; Sudo et al. 2004).
- Mitochondrial dysfunction: Mitochondrial dysfunction, characterized by impaired energy production and distribution, is associated with several mental disorders (Morris et al. 2017). Nutritional compounds, including antioxidants and specific nutrients, can improve mitochondrial function, suggesting a link between diet, mitochondrial health, and mental health (Morris and Berk 2015; Wright et al. 2015).

These pathways underscore the complexity of the diet–mental health relationship, highlighting the potential of Nutritional Psychiatry to offer novel insights and interventions. By understanding and harnessing these mechanisms, Nutritional Psychiatry aims to develop dietary strategies that complement traditional treatments, offering hope for more holistic and effective mental health care.

22.3 Overview of Key Nutrients Implicated in Mental Health

The intricate interplay between diet and mental health is underscored by the role of specific nutrients in brain function. This overview distils the essence of key macronutrients and micronutrients essential for mental well-being, drawing on foundational and contemporary research in the field (Table 22.1).

22.3.1 Macronutrients: A Foundation for Brain Health

- Amino acids: The building blocks of proteins, amino acids like tryptophan, methionine, and serine, are crucial for neurotransmitter synthesis and brain function (Heine 2000; Panula and Nuutinen 2013). Tryptophan, for instance, is a precursor to serotonin and melatonin, influencing mood, appetite, and sleep–wake cycles (Jenkins et al. 2016). Glycine and L-arginine play roles in synaptic

Table 22.1 Key nutrients and their impact on brain health and mental well-being

Nutrient type	Nutrient	Role in brain health	Impact on mental health	Key references
Macronutrients	Amino acids (tryptophan, methionine, serine)	Precursors to neurotransmitters, influence mood, appetite, sleep	Supports cognitive functions, mood regulation	Heine (2000), Panula and Nuutinen (2013)
	Fatty acids (omega-3s, SCFAs, MCFAs)	Maintain neuronal membrane, energy metabolism, neuroprotection	Influences cognitive abilities, mental health	Chang et al. (2020), Lei et al. (2016)
Micronutrients	Vitamin A	Neurogenesis, synaptic plasticity	Influences cognitive functions, memory	Olson and Mello (2010)
	B vitamins (B1, B3, B6, B9, B12)	Energy production, neurotransmitter formation	Impacts mood, cognitive functions	Calderón-Ospina and Nava-Mesa (2020)
	Vitamin D	Brain development, neuroplasticity, neurotransmitter regulation	Affects brain development, mood regulation	Tardy et al. (2020)
	Vitamin C and E	Antioxidants, protect neural tissues from oxidative stress	Supports brain health, prevents neurodegenerative changes	Muller (2010)
	Minerals (iron, zinc, magnesium)	Neurotransmitter production, synaptic transmission	Linked to cognitive function, risk of mental health disorders	Takeda (2003), Wang et al. (2018)
	Calcium and copper	Neuron signaling, neuroprotection	Associated with neurodevelopmental, neurodegenerative disorders	Schram et al. (2007)

transmission and neuroprotection, highlighting the importance of protein-rich diets in supporting cognitive functions and mental health (Bernstein et al. 2005; de Bartolomeis et al. 2020; McDearmid et al. 2006).

- Fatty acids: The brain's structural integrity depends significantly on fatty acids, particularly polyunsaturated fatty acids (PUFAs) like omega-3s (Chang et al. 2020). These fats are essential for maintaining neuronal membrane fluidity and function, influencing cognitive abilities and mental health (Lei et al. 2016). Short-chain fatty acids (SCFAs) derived from gut microbiota metabolism of dietary fibers impact the blood-brain barrier and neuroinflammation, whereas medium-chain fatty acids (MCFAs) and long-chain PUFAs are involved in energy metabolism and neuroprotection (Frost et al. 2014; Page et al. 2009; Yamawaki et al. 2018).

22.3.2 Micronutrients: Essential Vitamins and Minerals

22.3.2.1 Vitamins

- *Vitamin A*: Critical for neurogenesis and synaptic plasticity, vitamin A influences cognitive functions and memory (Olson and Mello 2010).
- *B vitamins*: A suite of B vitamins, including B1 (thiamine), B3 (niacin), B6, B9 (folate), and B12, are vital for energy production, DNA synthesis, and the formation of neurotransmitters, directly impacting mood and cognitive functions (Calderón-Ospina and Nava-Mesa 2020; Gómez-Pinilla 2008).
- *Vitamin D*: Often referred to as a neurosteroid, vitamin D plays a pivotal role in brain development, neuroplasticity, and regulation of neurotransmitters like dopamine (Tardy et al. 2020).
- *Vitamin C and E*: These antioxidant vitamins protect neural tissues from oxidative stress and inflammation, crucial for preventing neurodegenerative changes and supporting overall brain health (Muller 2010; Tardy et al. 2020).

22.3.2.2 Minerals

- *Iron, zinc, and magnesium*: Essential for neurotransmitter production, synaptic transmission, and protection against excitotoxicity (Takeda 2003; Wang et al. 2018). Deficiencies in these minerals are linked to cognitive impairments and increased risk of mental health disorders (Skalny et al. 2020).
- *Calcium and copper*: Play significant roles in neuron signaling and neuroprotection. Imbalances in these minerals can affect brain function and are associated with neurodevelopmental and neurodegenerative disorders (Schram et al. 2007; Tolppanen et al. 2011).

22.4 Methodological Approaches in Nutritional Psychiatry Research

Nutritional Psychiatry, an emerging field that explores the relationship between nutrition and mental health, employs various research methodologies to investigate this complex interaction. Here, we delve into the common research designs, the challenges faced by researchers in this domain, and the criteria used for evaluating the evidence.

22.4.1 Overview of Research Designs

- Observational studies: These studies observe and record participants' dietary patterns and mental health outcomes without intervention by the researchers (Zhang et al. 2023). They can provide insights into correlations between diet and mental health, but they cannot establish causality.
- Randomized controlled trials (RCTs): RCTs are considered the gold standard in nutritional psychiatry research (Marx et al. 2017). Participants are randomly assigned to intervention or control groups to receive specific dietary supplements or dietary interventions. These studies can establish causality and assess the effectiveness of nutritional interventions on mental health outcomes.
- Longitudinal studies: These studies follow participants over a period, often years, to observe how changes in diet affect mental health over time. They are valuable in understanding long-term impacts of nutrition on mental health (Adan et al. 2019; Marx et al. 2017).
- Cross-sectional studies: These studies examine the relationship between diet and mental health at a single point in time. While they can provide a snapshot of the current state, they cannot determine cause and effect (Phillips et al. 2018; Wattick et al. 2018).

22.4.2 Challenges and Limitations

- Dietary assessment accuracy: Accurately measuring dietary intake is challenging due to reliance on self-reported food frequency questionnaires, which are subject to recall bias (Rollo et al. 2016).
- Individual variability: Genetic differences, lifestyle factors, and environmental influences can affect individuals' responses to dietary interventions, making it difficult to generalize findings (Zuniga and McAuley 2015).
- Complexity of mental health disorders: Mental health conditions are influenced by a myriad of factors beyond diet, including genetics, environment, and lifestyle, complicating the isolation of dietary effects (Subar et al. 2015).
- Placebo effects: Especially in trials involving dietary supplements, the placebo effect can be significant, complicating the assessment of true intervention effects (Kirsch 2019; Weimer et al. 2015).

22.4.3 Criteria for Evaluating the Evidence

- Study design: Preference is given to well-designed RCTs for their ability to demonstrate causality(Marx et al. 2017).

- Sample size: Larger studies are more reliable as they can provide more statistically significant results and better represent the general population (Strickhouser et al. 2017).
- Follow-up duration: Longer follow-up periods in longitudinal studies offer more robust evidence of the long-term effects of dietary interventions on mental health (Davis et al. 2015).
- Replication: Studies that have been replicated with consistent results offer stronger evidence than those with findings that have not been duplicated (Davis et al. 2015).
- Bias and confounding factors: Studies that effectively manage potential biases and control for confounding variables are deemed more reliable (Fisher et al. 2016).
- Publication in peer-reviewed journals: Research published in reputable, peer-reviewed journals has undergone rigorous review, lending credibility to the findings (Tumin and Tobias 2019).

22.5 Evidence on Diet and Major Psychiatric Disorders

Below, we explore the evidence linking diet to several key mental health conditions (Table 22.2).

22.5.1 Depression

Dietary patterns: Research consistently links the Mediterranean diet, characterized by high consumption of fruits, vegetables, whole grains, and lean proteins, particularly fish, with lower rates of depression (Psaltopoulou et al. 2013; Sarris et al. 2014). The anti-inflammatory and antioxidant properties of this diet may protect against the neurobiological processes underlying depression (Estruch 2010; Schwingshackl and Hoffmann 2014).

Nutrient focus: Omega-3 fatty acids, found abundantly in fish oil, have shown promise in alleviating symptoms of depression, likely due to their anti-inflammatory effects on the brain (Chang et al. 2020). Additionally, deficiencies in B vitamins, particularly folate and B12, have been correlated with increased depression risk, suggesting their role in neurotransmitter synthesis and mood regulation (Calderón-Ospina and Nava-Mesa 2020).

Table 22.2 Dietary influences on different psychiatric disorders

Psychiatric disorder	Dietary patterns	Nutrient focus	Impact/evidence	Key references
Depression	Mediterranean diet: High in fruits, vegetables, whole grains, lean proteins	Omega-3 fatty acids, B vitamins (folate, B12)	Linked to lower rates of depression; nutrients may alleviate symptoms	Psaltopoulou et al. (2013), Sarris et al. (2014)
Anxiety disorders	Low in processed foods, high in antioxidants; ketogenic diet	Zinc, omega-3 fatty acids	May reduce anxiety symptoms; affects stress response systems	Bostock et al. (2017), Opie et al. (2015)
Schizophrenia	Focus on nutrient supplementation rather than patterns	Omega-3 fatty acids, antioxidants, vitamin D	May reduce symptoms or delay progression; addresses oxidative stress	Cha and Yang (2020), Frajerman et al. (2021)
Bipolar disorder	Fruits, vegetables, whole grains, lean proteins	Omega-3 fatty acids	Supports brain health; may stabilize mood and reduce depressive episode severity	Gabriel et al. (2023), Saunders et al. (2016)
ADHD	Elimination diets, low processed foods/ sugar, high omega-3	Omega-3 fatty acids, zinc, magnesium, iron	Mixed results; may improve attention and behavioral symptoms	Huberts-Bosch et al. (2023)

22.5.2 Anxiety Disorders

Dietary intervention: While less studied than depression, there is emerging evidence that diets low in processed foods and high in antioxidants may reduce anxiety symptoms (Opie et al. 2015). The ketogenic diet, known for its high-fat, low-carbohydrate ratio, has also shown potential in reducing anxiety in some studies, possibly by altering energy metabolism in the brain (Bostock et al. 2017; Sussman et al. 2015).

Nutrient focus: Zinc and omega-3 fatty acids have been studied for their potential to alleviate anxiety (Wang et al. 2018). These nutrients are thought to affect the brain's stress response systems and neurotransmitter levels.

22.5.3 Schizophrenia

Dietary patterns: Nutritional interventions in schizophrenia have focused less on dietary patterns and more on specific nutrient supplementation, such as omega-3 fatty acids, which may help reduce symptoms or delay the progression of the disorder in its early stages (Frajerman et al. 2021).

Nutrient focus: Antioxidants and anti-inflammatory nutrients are of interest due to the oxidative stress and inflammation observed in schizophrenia (Cha and Yang 2020; Matrisciano 2023). Vitamin D deficiency has also been noted in individuals with schizophrenia, suggesting a potential role for supplementation (Mitra et al. 2017).

22.5.4 Bipolar Disorder

Dietary patterns: Similar to other psychiatric disorders, a diet rich in fruits, vegetables, whole grains, and lean proteins may support overall brain health in bipolar disorder (Gabriel et al. 2023). However, specific dietary patterns targeting bipolar disorder have not been well studied.

Nutrient focus: Omega-3 fatty acids have received attention for their potential to stabilize mood in bipolar disorder, with some studies suggesting a benefit in reducing the severity of depressive episodes (Gabriel et al. 2023; Saunders et al. 2016).

22.5.5 ADHD

Dietary interventions: Elimination diets that remove potential allergens and additives are frequently explored for ADHD, with mixed results (Huberts-Bosch et al. 2023). Diets emphasizing the reduction of processed foods and sugar while increasing omega-3 fatty acid intake may improve symptoms.

Nutrient focus: Omega-3 supplementation has shown some promise in improving attention and behavioral symptoms associated with ADHD. Micronutrients, including zinc, magnesium, and iron, have also been studied due to their roles in neurotransmitter synthesis and brain function.

22.5.6 Nutritional Interventions in Psychiatry

Nutritional interventions in psychiatry represent a promising frontier, yet evidence from randomized controlled trials (RCTs) remains scarce. Among the interventions tested, the Mediterranean diet has garnered attention for its potential benefits. Notably, a 12-week Mediterranean diet intervention demonstrated significant improvements in mood and reduced anxiety levels among adults with major depression (Jacka et al. 2017). Subsequent RCTs, including the HELFIMED and PREDI_DEP trials, reinforced the positive impact of Mediterranean-style diets on mental health in depression (Parletta et al. 2019). Conversely, multinutrient supplementation in the MooDFOOD RCT did not alleviate major depression episodes in

overweight or obese adults with subsyndromal depressive symptoms, underscoring the need for further research (Bot et al. 2019).

The importance of early-life nutrition cannot be overstated, with evidence suggesting that interventions during the first 1000 days from conception play a pivotal role in later mental health outcomes. Nutrients crucial for neurodevelopment, including protein, iron, choline, folate, iodine, and various vitamins, influence cognitive function and may mitigate the risk of neurological impairments (Georgieff et al. 2018). Additionally, omega-3 and omega-6 polyunsaturated fatty acids have emerged as key players in brain development, with studies indicating their positive effects on neuronal membrane integrity and cognitive function (Freedman et al. 2018).

In adulthood and later life, dietary quality has been linked to cognitive decline, with evidence suggesting that adherence to a Mediterranean diet or increased intake of antioxidant polyphenols may mitigate age-related cognitive impairment (Valls-Pedret et al. 2015). Conversely, unbalanced diets, particularly those high in fat and sugar, have been associated with cognitive deficits and mood disorders, highlighting the intricate interplay between diet, metabolism, and mental well-being (Caruso et al. 2022; Siervo et al. 2021).

Recent insights into the gut–brain axis underscore the role of the gut microbiome in mental health (Berding et al. 2021). Alterations in gut microbiota composition have been linked to psychiatric disorders, stress responses, and cognitive function (Berding et al. 2021). Dietary factors, including high-fiber and Mediterranean diets, can modulate gut microbiota diversity, potentially influencing mental health outcomes (Mörkl et al. 2018).

Moving forward, a comprehensive understanding of the metabolic and cellular mechanisms underlying the effects of nutrition on mental health is imperative (Sandhu et al. 2017). Experimental medicine approaches, coupled with large-scale cohort studies, hold promise in elucidating these mechanisms and identifying personalized dietary interventions tailored to individuals' genetic predispositions and metabolic profiles (Oriach et al. 2016).

22.5.7 Comparison with Traditional Psychiatric Treatments

Nutritional interventions in psychiatry offer several advantages over traditional psychiatric treatments, including:

(a) Fewer side effects: Compared to pharmacotherapy, dietary interventions often have fewer adverse effects, making them attractive options for individuals who cannot tolerate or prefer to avoid medications (Opie et al. 2015).
(b) Holistic approach: Nutritional interventions target underlying physiological mechanisms implicated in psychiatric disorders, offering a holistic approach to treatment that complements traditional therapies (Hollis et al. 2017; Hosker et al. 2019).

(c) Potential for prevention: Dietary modifications have the potential to prevent the onset or recurrence of psychiatric symptoms, providing long-term benefits for mental health and overall well-being (Teasdale et al. 2017).

22.6 Challenges and Future Directions in Nutritional Psychiatry

22.6.1 Complexity of Diet–Brain–Behavior Relationships

The field of Nutritional Psychiatry is grappling with the intricate and multifaceted relationships between diet, brain function, and behavior (Smith 2020). These relationships are complex due to the interplay of numerous factors, including genetic predispositions, environmental influences, and individual lifestyle choices (Smith and James 2023). The brain's response to dietary inputs is nuanced, mediated by various biological pathways such as inflammation, oxidative stress, neuroplasticity, and the gut–brain axis (Sarris 2019). Understanding these pathways requires sophisticated research methodologies and interdisciplinary collaboration. Moreover, the subjective nature of mental health disorders adds another layer of complexity, making it challenging to establish clear causal links between diet and psychiatric conditions (Sarris 2019).

22.6.2 Nutritional Recommendations in Psychiatric Practice

Integrating nutritional recommendations into psychiatric practice presents several challenges. First, there is a need for clinicians to be adequately trained in nutrition science and its application to mental health. Currently, many psychiatrists and mental health professionals lack comprehensive training in this area, limiting their ability to offer evidence-based dietary advice (Jacka 2017). Second, the variability in individual responses to dietary interventions necessitates a personalized approach, which can be difficult to standardize in clinical settings (Bush et al. 2020). Additionally, dietary advice must be culturally sensitive and consider socioeconomic factors that affect individuals' food choices and access to healthy food options (Monterrosa et al. 2020).

22.6.3 The Need for Personalized Nutrition Approaches in Mental Health Care

Personalized nutrition, which tailors dietary recommendations to an individual's genetic, metabolic, and microbiome profile, holds great promise for mental health care. However, implementing personalized nutrition approaches faces several hurdles (Bush et al. 2020). These include the cost and accessibility of genetic and microbiome testing, the need for advanced computational tools to analyze complex data, and the challenge of integrating this information into practical dietary advice (Bush et al. 2020). Furthermore, ethical considerations arise regarding privacy and the potential for genetic discrimination. Despite these challenges, personalized nutrition offers the potential for more effective and targeted interventions, underscoring the need for continued research and development in this area.

22.6.4 Emerging Areas of Research

Nutrigenomics, the study of how diet interacts with genes to affect health, is an emerging area of research with significant implications for Nutritional Psychiatry (Grajek et al. 2022). By understanding how specific nutrients influence gene expression related to brain function and mental health, researchers can develop more targeted dietary interventions (Larroya et al. 2021). Other promising areas include the exploration of novel biomarkers for mental health disorders, which could improve diagnosis and treatment outcomes, and the study of psychobiotics, which focuses on how probiotics and prebiotics can affect mental well-being through the gut–brain axis (Colica et al. 2017).

22.7 Practical Implications for Clinicians and Patients

22.7.1 Guidelines for Incorporating Nutritional Psychiatry into Practice

(a) Educational advancement: Clinicians should seek to enhance their understanding of Nutritional Psychiatry through continued education and training. This can involve attending workshops, webinars, and conferences, or engaging with the latest research findings in this area.
(b) Comprehensive assessments: Incorporate nutritional assessments into routine psychiatric evaluations. This involves asking patients about their dietary habits, preferences, and any food intolerances or allergies, to identify potential areas for intervention.

(c) Interdisciplinary collaboration: Work closely with dietitians, nutritionists, and other healthcare professionals to develop comprehensive, multidisciplinary care plans that address both the mental and nutritional needs of patients.
(d) Individualized recommendations: Tailor dietary advice to the individual needs, preferences, and socioeconomic status of patients, considering cultural relevance and accessibility of recommended foods.
(e) Monitoring and follow-up: Regularly monitor patients' progress and adjust dietary recommendations as needed, based on their mental health status and any changes in their physical health or medication regimen.

22.7.2 Recommendations for Patients on Optimizing Diet for Mental Health

(a) Prioritize whole foods: Emphasize a diet rich in fruits, vegetables, whole grains, lean proteins, and healthy fats, particularly those high in omega-3 fatty acids, such as fish, nuts, and seeds.
(b) Limit processed foods: Reduce intake of processed, sugary, and high-fat foods, which have been linked to poorer mental health outcomes.
(c) Stay hydrated: Ensure adequate fluid intake, focusing on water and minimizing high-sugar or caffeinated beverages, which can impact mood and energy levels.
(d) Consider nutrient supplementation: Based on healthcare advice, consider supplementation with key nutrients that support mental health, such as omega-3 fatty acids, B vitamins, and vitamin D, particularly if dietary intake may be lacking.
(e) Mindful eating practices: Engage in mindful eating practices to enhance the enjoyment of food and improve dietary habits, paying attention to hunger and satiety cues.

22.8 Summary and Conclusion

The field of Nutritional Psychiatry (NP) represents a groundbreaking intersection of nutrition and mental health, offering a novel lens through which to view the prevention and treatment of psychiatric disorders. This chapter has provided a comprehensive exploration of NP, highlighting its potential to revolutionize mental health care by integrating dietary modifications and targeted nutrient supplementation alongside traditional treatments. By elucidating the theoretical underpinnings and biological mechanisms—such as inflammation, oxidative stress, neuroplasticity, and the gut–brain axis—that link diet to mental health, it underscores the importance of diet quality as a modifiable risk factor for mental disorders.

Evidence presented in the chapter indicates that dietary patterns rich in whole foods and low in processed foods correlate with better mental health outcomes, suggesting that nutrition could play a pivotal role in managing conditions like depression, anxiety, schizophrenia, bipolar disorder, and ADHD. However, the integration of NP into psychiatric practice is still emerging, faced with challenges that include the need for further clinician education, standardized nutritional assessment guidelines, and more rigorous research to solidify the evidence base. In conclusion, NP offers a promising and holistic approach to mental health care, emphasizing the need for a personalized and multidisciplinary treatment strategy. The chapter calls for concerted efforts in research, clinical practice, and policy to embrace and advance the field of NP. As we continue to uncover the complex relationship between diet and mental health, NP holds the potential to enrich our therapeutic toolkit, offering new pathways for enhancing patient care and ultimately improving mental health outcomes.

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