Annual Review of Food Science and Technology

From Fork to Feelings: How Foods Shape Mental Health via the Microbiota–Gut–Brain Axis

Aimone Ferri,[1,2,3] Laise Trindade Paes,[1] Elizabeth Schneider,[1] Gerard Clarke,[1,3] and John F. Cryan[1,2]

[1]APC Microbiome Ireland, Cork, Ireland

[2]Department of Anatomy and Neuroscience, University College Cork, Cork, Ireland; email: j.cryan@ucc.ie

[3]Department of Psychiatry and Neurobehavioural Science, University College Cork, Cork, Ireland

Annu. Rev. Food Sci. Technol. 2026. 17:181–207

First published as a Review in Advance on February 2, 2026

The *Annual Review of Food Science and Technology* is online at food.annualreviews.org

https://doi.org/10.1146/annurev-food-053124-110137

Keywords

microbiota–gut–brain axis, diet, mental health, fermented food, nutritional psychiatry, psychobiotic

Abstract

The microbiota–gut–brain axis, defined as the bidirectional communication linking the gut microbiota with the brain, operates through neural, metabolic, immune, and endocrine signals. It plays an important role in mental health, regulating stress response, mood, and cognitive function, and is altered in psychiatric conditions. Although the gut microbiota remains stable during healthy adulthood, it is modifiable by lifestyle, medication, and diet, making it a tractable target for mental health interventions. Diet is emerging as a viable option to improve mental health through gut microbiota modulation. Energy-dense, high-fat, and high-sugar diets have been linked to poor mental health, whereas Mediterranean, fiber-rich, and fermented-food diets show benefits, possibly through provision of specific nutrients and beneficial microbial metabolites such as short-chain fatty acids. However, more human research addressing variability and confounding is needed to unlock these mechanisms and support personalized/precision nutrition. This review discusses current evidence and proposes multidisciplinary, rigorous diet–microbiota–mental health research.

INTRODUCTION

Mental health disorders are among the leading causes of global disability, with rising prevalence across age groups and geographical regions (GBD 2019 Mental Disorders Collaborators 2022). Despite increased pharmacotherapeutic options, treatment outcomes remain suboptimal for many individuals (Cipriani et al. 2018). In this context, there is growing interest in modifiable lifestyle factors, such as diet, as potential adjunctive or preventive strategies in mental health care. Indeed, the field of nutritional psychiatry has emerged as a key area offering tangible strategies for how diet can be harnessed for mental health benefits (Jacka 2017). However, the mechanisms through which diet could modulate mental health conditions are only partially elucidated.

One of the most exciting areas to emerge in the past decades is the potential for the gut microbiota (the trillions of microorganisms inhabiting the gastrointestinal tract) to be a key conduit for how diet affects the host. The human diet shapes the gut microbiota through complex interactions, demanding a systematic and comprehensive approach to understanding this relationship (Diacova et al. 2025). The gut microbiota plays an important role in host health by synthesizing neuroactive compounds, modulating immune responses (O'Riordan et al. 2025), and influencing nutrient metabolism (Sanz et al. 2025). Additionally, the gut microbiota is a key component of the gut–brain axis, a bidirectional communication system linking the gut and the central nervous system (CNS) through neural, endocrine, and immune pathways, including the hypothalamic–pituitary–adrenal (HPA) axis (Cryan et al. 2019). Given the capacity of gut microbiota to change in response to diet, it represents a key mechanism through which diet may influence mental health. This review aims to provide a critical overview of how foods and diet affect mental health via the gut microbiome by summarizing current knowledge on diet–microbiome interactions and microbiome alterations in mental health and discussing dietary strategies with the potential to modulate the gut–brain axis. Furthermore, the review highlights methodological limitations and challenges, and provides considerations and future directions for advancing the field.

DIET AND THE GUT MICROBIOME

Dietary patterns are key modulators of gut microbiota composition and function, impacting overall health indices through direct nutritional effects and microbial-driven mechanisms. Environmental factors, geographical differences, and genetics contribute alongside diet in shaping the gut microbiome, but specific microbial profiles connect diet and host metabolism (Asnicar et al. 2021).

Plant-Based Diets

Plant-based diets are an umbrella term to describe diets characterized by high intake of foods rich in fiber, polyphenols, and bioactive compounds and low in saturated fats and that have been linked to beneficial changes in gut microbiota, including a greater abundance of fiber-degrading bacteria. Recent metagenomic data from more than 21,000 individuals revealed that vegan and vegetarian diets are associated with higher levels of short-chain fatty acid (SCFA)-producing taxa such as *Butyricicoccus* sp., *Lachnospiraceae*, and *Ruminococcus hominis*, whereas omnivorous diets, particularly those rich in red meat, were enriched in proinflammatory species such as *Bilophila wadsworthia*, *Alistipes putredinis*, and *Ruminococcus torques*, which have been linked to adverse cardiometabolic outcomes (Fackelmann et al. 2025). There are notable overlaps between the Mediterranean diet and plant-based diets, as both have been shown to be protective against cardiovascular diseases (Hareer et al. 2025) and development of depression (Lee et al. 2025). Additionally, a hallmark of these diets is their high fiber content, which may lead to similar modulatory effects on gut microbiota. For instance, increased relative abundance of the genus *Prevotella* is favored in vegan and vegetarian diets due to its ability to degrade dietary fibers (Trefflich et al. 2020).

The Mediterranean Diet

The Mediterranean diet, which is rich in fruits, vegetables, whole grains, legumes, fish, extra virgin olive oil, and low intake of red meats, has been consistently associated with reduced risk of cardiometabolic diseases, cancer, cognitive decline, and improved quality of life (Guasch-Ferré & Willett 2021). Long-term adherence to a Mediterranean-style diet induces subtle yet meaningful shifts in the gut microbiome, favoring an expansion of beneficial taxa such as *Prevotella*, *Faecalibacterium prausnitzii*, *Bacteroides cellulosilyticus*, and *Roseburia* spp. while reducing *Collinsella aerofaciens* and *Ruminococcus torques* (Wang et al. 2021). These compositional microbial changes lead to functional benefits such as enhanced capacity for fiber degradation, SCFA production, and bile acid metabolism, mechanisms potentially contributing to its cardiometabolic benefits.

Western Diet and Processed Foods

On the other hand, unhealthy dietary patterns, colloquially identified as the Western diet (WD), are characterized by heavy consumption of animal products, processed meats, added sugar, sodium, and saturated fats, and they are poor in their plant-based components such as fruits and vegetables (Azzam 2021). In recent years, the Nova classification system has been proposed to categorize foods based on their degree of processing, with ultraprocessed foods (UPFs) identified as a central component of WDs. UPFs are characterized by additional ingredients such as flavorings, emulsifiers, colorings, and preservatives and are designed to be hyperpalatable, convenient, and shelf stable. They are typically energy-dense, high in added sugars, fats, and salt, and low in fiber and micronutrients, contributing to adverse health outcomes (Monteiro et al. 2019). The WD is associated with chronic low-grade inflammation, metabolic disturbances, an altered gut microbiome with reduced diversity and functionality, and lower SCFA production (Ross et al. 2024). Gut microbiota changes associated with WDs often show a striking depletion of the relative abundance of *Prevotella copri* and increased relative abundances of *Bacteroides*, *Ruminococcus*, *Faecalibacterium*, *Alistipes*, *Blautia*, and *Bilophila* (Ross et al. 2024).

High-Protein Diets

High-protein diets, often defined as diets in which target protein intake is increased from recommended dietary allowance levels up to 3 g/kg of bodyweight, are used to prevent and reverse lean mass loss, increase satiety, and enhance recovery and promote a positive nitrogen balance in sports nutrition (Jäger et al. 2017). Once undigested proteins reach the colon, they undergo microbial fermentation, influencing gut microbiota composition and metabolic activity, depending on protein digestibility and amino acid profile. These diets are associated with an increased abundance of proteolytic bacteria, including *Propionibacterium*, *Clostridium*, *Bacillus*, and *Fusobacterium*, along with microbes that thrive on amino acid metabolites via cross-feeding (Ross et al. 2024). A study in individuals with obesity or overweight reported increased microbial diversity, higher relative abundances of *Akkermansia* and *Bifidobacterium*, and reduced *Prevotella*, underscoring the high-protein diet's potential to modulate gut communities and confer metabolic benefits (Dong et al. 2020). Athletes across multiple disciplines following high-protein diets display specific differences in the gut microbiome, and they represent a unique demographic group, as they also have high intakes of carbohydrates and fiber as well, which is reflected in increased *Prevotella* (Mohr et al. 2020).

Ketogenic Diets

Ketogenic diets (KDs) are characterized by low carbohydrate (often less than 50 g/day), moderate protein, and moderate to high fat intake, which shifts body metabolism toward fat oxidation and the production of ketone bodies (Kossoff et al. 2018). KDs have unique properties, including anti-inflammatory and epigenetic effects, and they can be extensively metabolized by the CNS (Anderson et al. 2024). KDs were originally developed more than a century ago as an alternative to fasting for children with epilepsy after it was noticed that this can reduce seizures in some patients, before the discovery of anticonvulsant medications, and they are still used today (Kossoff et al. 2018). KDs have been successfully and safely used to treat obesity and related metabolic disorders (Barrea et al. 2022), but they also have been explored as a therapeutic intervention for several neuropsychiatric disorders (Anderson et al. 2024). KDs modulate the gut microbiota differently than a typical high-fat diet by reducing Actinobacteria and Firmicutes, including several *Bifidobacterium* species, while increasing *Bacteroidetes*, a shift linked to the host-derived ketone body production (Ang et al. 2020). Moreover, in children with drug-resistant epilepsy, a six-month KD decreased the abundance of epileptic-associated genera, *Bifidobacterium*, *Akkermansia*, *Enterococcaceae*, and *Actinomyces*, which correlated with symptom improvement and increased fecal SCFA content (Gong et al. 2021). Preclinical work supports an active role of the gut microbiome in mediating the antiepileptic effects of a KD. A study using a mouse model of epilepsy showed that the gut microbial changes induced by a KD were sufficient to confer seizure resistance, which was also mirrored in increased hippocampal γ-aminobutyric acid (GABA) levels (Olson et al. 2018). Furthermore, another study demonstrated that when inoculated with the fecal microbiota from pediatric refractory epilepsy patients, mice on a standard diet had increased susceptibility to seizures, whereas transplanting the fecal microbiota of the same patients after a KD effectively increased seizure resistance and produced a specific metabolic signature (Lum et al. 2023).

Diet, the Gut Microbiota, and the Need to Contextualize Dietary Components Within Whole Diets

To summarize, dietary patterns are associated with distinct gut microbial signatures, despite the considerable influence of genetics and environmental factors on the gut microbiota. Diet represents a key modifiable factor, and although dietary patterns are made of numerous foods, certain specific features, such as extra virgin olive oil in the Mediterranean diet, can be used to differentiate them. Nonetheless, considerable overlap exists among health-promoting diets, for example, high fiber content, increased polyphenol intake, and low consumption of energy-dense processed foods, which can be common factors between the Mediterranean diet and more general plant-based diets. The beneficial effects of the Mediterranean diet are likely mediated in part by these shared components, even though these features are not directly captured in scoring systems. Consequently, to understand the complex relationship between diet, the gut microbiome, and health, it is necessary to examine both foods and specific nutrients without losing sight of the broader overview of the matrices and contexts in which these components are delivered during habitual whole diet intakes. The following sections first review current evidence linking the gut microbiome with mental health and then explore how diet can influence this relationship through modulation of the microbiota–gut–brain axis.

THE GUT MICROBIOME AT THE INTERSECTION OF DIET AND MENTAL HEALTH

Mental health conditions such as depressive disorders, anxiety disorders, bipolar disorders (BDs), schizophrenia spectrum disorders (SSDs), and attention-deficit hyperactivity disorder (ADHD) are among the most prevalent mental health disorders, and they are often comorbid with physical illnesses, including metabolic and cardiovascular diseases (GBD 2019 Mental Disorders Collaborators 2022). These disorders frequently emerge early in life and contribute to substantial personal and societal burden (Solmi et al. 2022). Although their pathophysiology is complex and multifaceted, growing evidence points to an involvement of the gut microbiome.

Systematic reviews of observational studies have identified altered microbial communities in individuals with mental health disorders, typically characterized by a depletion of beneficial taxa (e.g., *Faecalibacterium*, *Coprococcus*), alteration in neurotransmitter-producing taxa, and an enrichment of taxa associated with inflammation or disrupted metabolism (McGuinness et al. 2022). Moreover, irritable bowel syndrome is highly prevalent across all mental health conditions, affects symptom severity, and further highlights the involvement of the gut–brain axis (Zhang et al. 2024). Taken together, these findings suggest a potential role of the gut microbiome in the pathogenesis or maintenance of psychiatric symptoms.

Finally, although diagnostic categories serve clinical utility, symptom overlap across disorders and heterogeneity within them suggest that a transdiagnostic approach may better capture mechanisms through which the microbiota–gut–brain axis is involved in mental health (Kelly et al. 2018). This section reviews the evidence linking diet, mental health, and the gut microbiome. An overview of shared and disorder-specific features is provided in **Table 1**.

Diet and Mental Health

The relationship between diet and mental health has become an area of growing interest, and although mental health conditions can influence food choices, a growing body of evidence points toward diet as a modifiable factor affecting mental health (Ribeiro et al. 2022). Numerous observational studies link healthy dietary patterns to better mental health. Dietary patterns such as the Mediterranean diet and diets rich in fruits and vegetables contribute to decreased risk of developing depression in adults (Matison et al. 2021). Similarly, higher dietary quality, which is reflected by high intake of fruits and vegetables and moderate intake of animal-based products, was found to be inversely associated with depression in a large sample of younger adults (Ogden et al. 2025). Although most of the research focuses on depression, emerging evidence suggests broader implications of diet on mental health. For instance, higher dietary quality has been linked to improved symptom profiles and treatment response in individuals with BDs (Ashton et al. 2020), and dietary patterns rich in fruits and vegetables have been found to be associated with reduced odds of ADHD (Shareghfarid et al. 2020).

In addition to observational studies, several randomized controlled trials (RCTs) provide evidence of healthy diets supporting mental health. An RCT demonstrated that a modified Mediterranean diet induced a clinically meaningful and superior reduction in depressive symptoms compared to a control social support intervention (Jacka et al. 2017). Furthermore, another RCT showed that the beneficial effects of the Mediterranean diet can be extended to young adults with moderate to severe depression (Bayes et al. 2022). Moreover, a comprehensive lifestyle intervention that includes multiple sessions of dietary education has been shown to be noninferior to psychotherapy in improving depressive symptoms, further strengthening the potential of nutritional interventions in mental health care (O'Neil et al. 2024). Mechanistically, healthy diets may improve mental health through correcting suboptimal intakes of macro- and micronutrients. Also, increased intake of beneficial compounds such as antioxidants improved metabolic health and reduced chronic low-grade inflammation, which is often found to be increased in mental health conditions (Yuan et al. 2019). Additionally, one RCT employing a gut-targeted diet rich in prebiotic and fermented foods showed an improvement in perceived stress, with greater benefits observed among individuals with a more stable and less volatile microbiota, suggesting that the gut microbiome is involved as well (Berding et al. 2023).

Although observational research can suffer from reverse causality and residual confounding, consistent associations and emerging mechanistic data and evidence from RCTs strengthen the case for healthy diets as a contributing factor to mental health outcomes.

Table 1 Overview of mental health condition symptoms, their treatment, side effects, and common physical and psychiatric comorbidities

Mental health condition	Main symptoms	Common comorbidities	HPA axis and inflammation	Gut microbiota	References
Depressive disorders	Mood dysregulation, anhedonia	Anxiety disorders, metabolic disorders, sleep disorders, IBS	↑↓ HPA axis reactivity, ↑ daily cortisol, depending on the presence of adverse childhood events and depression phenotype ↑ Inflammation	↓ *Ruminococcus*, *Faecalibacterium*, *Roseburia*, *Prevotella*, *Coprococcus*, *Butyricicoccus* ↑ *Lactobacillus*, *Eggerthella*, *Streptococcus* No differences in α-diversity, β-diversity related to medication use	Dilmore et al. 2025, Goldsmith et al. 2016
Anxiety disorders	Persistent, excessive worry or fear	Depressive disorders, metabolic disorders, sleep disorders, IBS	↓ HPA axis reactivity ↑ Daily cortisol No consistent findings linking inflammation and anxiety disorders	↓ *Ruminococcus*, *Coprococcus*, *Faecalibacterium* ↑ *Eggerthella* No differences in α-diversity or separation metrics (β-diversity) even after accounting for medication use.	Butler et al. 2025, Dilmore et al. 2025, Zorn et al. 2017
ADHD	Inattention and/or hyperactivity–impulsivity causing functional impairment, with symptom onset before age 12	Depressive disorders, bipolar disorders, anxiety disorders, metabolic disorders, sleep disorders, autism spectrum disorder, obsessive-compulsive disorders, IBS	= or ↑ HPA axis reactivity = or ↓ daily cortisol ↓↑ Inflammation, depending on phenotype, age, and medication use	↑↓ *Ruminococcus gnavus* ↑ *Odoribacter*, *Enterococcus* ↓ *Faecalibacterium*, *Veillonellaceae* ↓ SCFA, especially with medication use No differences in α-diversity; β-diversity related to differences in habitual diet.	Chang et al. 2021, Stiernborg et al. 2023
Bipolar disorders	Periods of abnormally elevated or irritable mood, it can include depressive episodes	Anxiety disorders, ADHD, metabolic disorders, IBS	↓ HPA axis reactivity ↑ Daily cortisol, which correlates with symptom severity, especially preceding mania ↑ Inflammation	↓ *Faecalibacterium*, *Ruminococcus*, *Roseburia*, *Coprococcus* ↑ *Lactobacillus*, *Streptococcus*, *Eggerthella* Illness duration correlates with ↓ α-diversity ↓ *Faecalibacterium*, ↑ *Lactobacillus* and ↑ *Streptococcus* correlate with higher inflammation	Evans et al. 2017, van den Berg et al. 2020
Schizophrenia spectrum disorders	Delusions, hallucinations, disorganized thinking/behavior, blunted affect, anhedonia	Anxiety disorders, metabolic disorders, IBS	↓ HPA axis reactivity ↑ Daily cortisol ↑ Inflammation	↓ *Roseburia*, *Coprococcus* ↑ *Lactobacillus*, *Eggerthella*, *Prevotella*, *Succinivibrio* No differences in α-diversity, altered β-diversity *Succinivibrio* correlates with inflammation	Goldsmith et al. 2016, Murray et al. 2023, Quidé et al. 2021

Data on symptoms from American Psychiatric Association (2022).
Data on treatment, side effects, common physical, and psychiatric comorbidities from Bourque et al. (2024).
Abbreviations: ADHD, attention-deficit/hyperactivity disorder; HPA, hypothalamic–pituitary–adrenal; IBS, irritable bowel syndrome.

Poor Dietary Quality and Its Effects on Mental Health

Besides healthy dietary patterns, it is also important to consider diet from a compositional point of view: higher intake of health-promoting foods typically corresponds to lower intake of energy-dense, nutrient-poor foods, such as UPFs, and vice versa. Consumption of such foods is consistently associated with poorer mental health (Godos et al. 2023), with foods rich in added sugars and fats and poor in fiber being the most representative. Beyond their macronutrient content, UPFs are believed to exert additional negative effects on health due to food additives, emulsifiers, and disrupted food matrices, which may impair hunger–satiety regulation, metabolic health, and gut barrier integrity (Dicken & Batterham 2024), potentially contributing to both increased chronic low-grade inflammation and worsened mental health.

Added sugars, especially in the form of sugar-sweetened beverages, are well-known to impair metabolic health and increase adiposity and low-grade inflammation, and they are increasingly being associated with poorer mental health as well (Lane et al. 2024). Although the specific mechanisms through which sugar may affect mental health are still underexplored, it has been hypothesized that consumption of sugar-rich foods represents a self-medication strategy due to their dampening effect on stress reactivity, thus suggesting a bidirectional relationship between sugar and mental health that requires further research (Di Polito et al. 2023).

Another core aspect of unhealthy diets is increased fat intake, especially saturated fat, which is widely present in fatty and processed meats, savory fast foods, and pastries and desserts, which also contain high levels of added sugars. Saturated fat intake is linked to increased inflammatory status, and, indeed, observational studies show an association between higher dietary inflammatory potential and saturated fat intake with a higher risk of developing anxiety, depression, and neurological disorders (Fu et al. 2025). Moreover, the detrimental effects of high-fat diets on human health can be rapidly observed after a single meal. Feeding studies show increased postprandial inflammation, with saturated fats having a stronger proinflammatory effect when compared to unsaturated fats (Raz et al. 2013). Overall, inflammation represents one of the links between diet and mental health, but the gut microbiome is likely involved as well. This idea is supported by the effects of high consumption of these energy-dense and fiber-depleted foods on the gut microbiome, as decreased abundance of fiber-degrading commensals may impair the gut barrier function, further increasing endotoxemia, inflammation, and immune dysregulation (Sonnenburg & Sonnenburg 2014), thus potentially affecting mental health through the gut–brain axis.

MICROBIOTA–GUT–BRAIN AXIS COMMUNICATION: MECHANISMS OF ACTION

Several interconnected mechanisms underpin gut–brain axis communication (**Figure 1**), involving microbial metabolites, neural pathways, and host neuroendocrine systems; the main pathways are briefly outlined below.

Microbial Metabolites

The gut barrier, composed of a layer of tightly joined epithelial cells, serves as an interface where microbial metabolites interact with host immune cells, influencing local and systemic immune responses, gut barrier function, and neuroimmune signaling (Aburto & Cryan 2024). SCFAs comprise more than 95% of these gut microbial metabolites, with dietary fiber significantly contributing to their production. SCFAs serve as an energy source to colonocytes, thereby maintaining gut barrier integrity, but they also exert diverse immunomodulating and neuroactive effects by activating G-protein-coupled receptors and inhibiting histone deacetylases (HDACs) (O'Riordan et al. 2025).

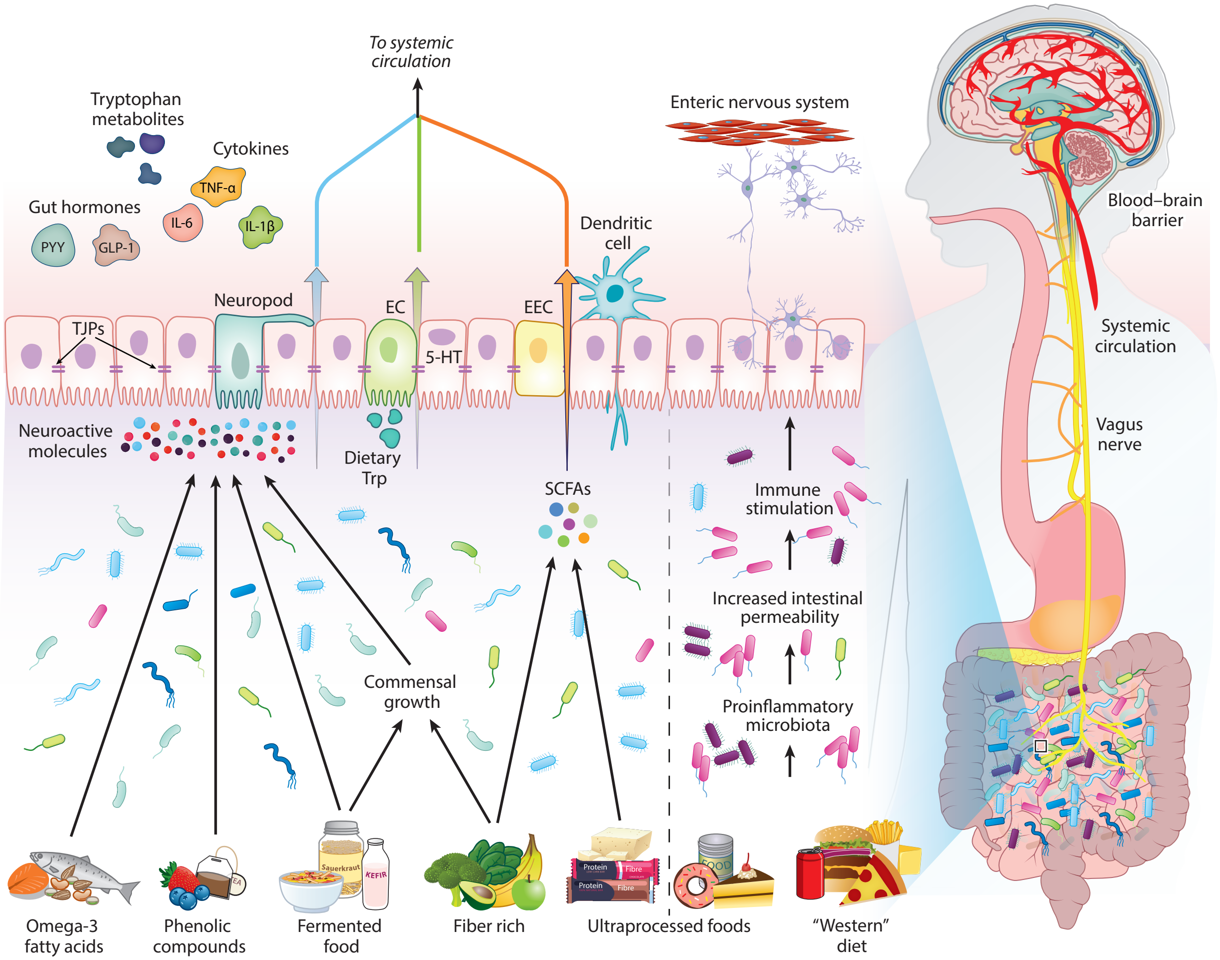


Figure 1

Mechanisms underlying the microbiota–gut–brain axis communication. The gut microbiota influences host physiology through the production of neuroactive compounds, short-chain fatty acids (SCFAs), and tryptophan metabolites, which interact with epithelial, enteroendocrine, immune, and neural cells. These signals can reach the central nervous system through systemic circulation or the vagus nerve, affecting brain function and behavior. Dietary factors can trigger the release of neuroactive peptides such as glucagon-like peptide 1 (GLP-1) from enteroendocrine cells (EEC) and shape the gut microbial ecology and gut barrier integrity. When this equilibrium is disrupted, it can trigger immune activation and release of proinflammatory cytokines such as interleukin-6 (IL-6), contributing to dysregulation of gut–brain signaling. Abbreviations: 5-HT, serotonin; EC, enterochromaffin; IL-1β, interleukin-1 beta; PYY, peptide YY; TJPs, tight junction proteins; TNF-α, tumor necrosis factor alpha.

Among these SCFAs, butyrate and, to a lesser extent, propionate inhibit HDACs, a class of enzymes heavily involved in epigenetic regulation of inflammatory response and antioxidant defense systems. These effects are particularly relevant to human health, including mental health, where a reduced abundance of key butyrate producers is observed alongside increased inflammatory markers (**Table 1**).

Additionally, other neurotransmitters produced in the gut include catecholamines, such as dopamine, adrenaline, and norepinephrine, which are involved in regulating gut function, mood, attention, motivation, and the stress response (Wiley et al. 2021). Catecholamines also mediate host–microbe interactions in the gut, where both enteric neurons and microbial enzymes contribute to their synthesis and activation. Furthermore, GABA, the main inhibitory neurotransmitter in the CNS, can be converted from glutamate by certain bacterial strains such as *Lactobacillus* and *Bifidobacterium* that appear to be differentially abundant across several mental health disorders (McGuinness et al. 2022).

Serotonin and Tryptophan

The gut–brain axis is also influenced by microbial modulation of the metabolism of amino acids, most notably tryptophan, the precursor to serotonin (5-HT) and other neuroactive metabolites (Gheorghe et al. 2019). 5-HT, primarily synthesized in the gut by enterochromaffin cells, influences gastrointestinal, immune, and neurological functions, with more than 90% of total body 5-HT produced peripherally and acting through diverse receptor subtypes across multiple systems. Although gut-derived serotonin may play a role in mood regulation via local actions in the gut, it cannot cross the blood–brain barrier, but the precursor tryptophan can enter the CNS via amino acid carriers and can be converted into serotonin, thereby influencing mood disorders (Hung et al. 2025). Nevertheless, the primary route of tryptophan metabolism is through the kynurenine pathway, responsible for approximately 90% of tryptophan degradation, which is tightly regulated by immune and neuroendocrine signals via enzymes, leading to the production of neuroactive metabolites like kynurenic acid and quinolinic acid (Kennedy et al. 2017). An altered tryptophan metabolism is evident in mental health conditions; for instance, plasma levels of these tryptophan catabolites were found to be altered in individuals with mental disorders, with partial normalization observed upon remission (Brum et al. 2023).

Vagus Nerve

The vagus nerve, a key conduit for bidirectional signaling between the gut and the brain, modulates not only gastrointestinal and immune functions but also emotional and behavioral responses (Fülling et al. 2019). As it plays a central role in coordinating gastrointestinal activity, dietary signals can reach the brain via this pathway, helping regulate food intake. Diets rich in fat and sugar have been shown to disrupt gut microbiota composition, contributing to gut inflammation and impaired vagal signaling, partly through increased intestinal permeability and neuroinflammatory changes, highlighting the gut microbiota's role in modulating this communication route (Sen et al. 2017). In mice, the observation that probiotics can alter behavior has raised the question of whether the gut microbiota can signal through the vagus nerve, offering a possible mechanism by which certain bacteria communicate with the brain, an idea supported by preclinical vagotomy studies (Bravo et al. 2011). Although human research is scarce, vagus nerve stimulation is gaining attention as a potential therapy for neuropsychiatric conditions, including severe forms of depression, highlighting its relevance in mental health (Jung et al. 2024). Finally, it has been recently shown that microbial flagellin can activate neuropod enteroendocrine cells that result in peptide YY (PYY) release and activation of the vagus nerve to modulate feeding. This "neurobiotic sense" offers an intriguing mechanism as to how the microbiome can affect complex behavior (Liu et al. 2025).

The Hypothalamic–Pituitary–Adrenal Axis

The HPA axis, a main regulator of the stress response, influences many body processes, including neuroendocrine function, immunity, inflammation, and digestion. Inflammatory cytokines stimulate CRH release, initiating the HPA axis activation that leads to cortisol release and suppression of inflammation. Meanwhile, the vagus nerve inhibits the HPA axis through its efferent fibers projecting to the hypothalamus (Agorastos et al. 2019). Under chronic stress conditions, prolonged

HPA axis stimulation impairs this feedback system, reducing the vagus nerve inhibitory effect, which contributes to elevated cortisol levels and diminished anti-inflammatory activity. The HPA axis is tightly linked to the gut–brain axis with bidirectional influences; microbial modulation of immune mediators such as TNF-α, IL-1β, and IL-6 can signal to the brain and activate this stress response (Cussotto et al. 2018). During early life, microbial colonization is essential for proper HPA axis maturation, and disruptions may lead to long-lasting alterations in stress responsiveness (Sudo et al. 2004). Moreover, gut dysbiosis has been associated with altered HPA axis activity, suggesting a link between microbial imbalance and chronic stress-related disorders (Cryan & Dinan 2012). There is increasing interest in modulating HPA axis activity through gut-targeted strategies, as SCFAs have been shown to modulate the stress response in humans (Dalile et al. 2020), thus indicating a potential for microbiota-mediated pathways. Recently, we have also shown that the microbiota is a key regulator of how the HPA axis is governed by circadian signals (Tofani et al. 2025). The implications for these findings reinforce that it may not be just what we feed our microbes, but also when we feed them. Together, these mechanisms reveal how gut–brain communication integrates microbial, immune, and neural signals to shape gastrointestinal and mental health.

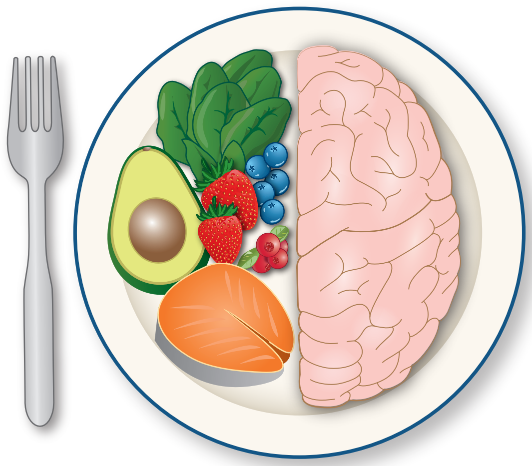
WHOLE FOODS AND THE MICROBIOTA–GUT–BRAIN AXIS: A RECIPE FOR MENTAL HEALTH

Combining observational evidence from large studies with evidence from RCTs and mechanistic studies is fundamental to synthesizing and advancing our evidence base for understanding the relationship between food, the gut microbiome, and mental health. Characteristic microbiome signatures are linked to dietary patterns and mental health conditions, and healthy diets are linked to improved mental health outcomes. Specific dietary components, shown in **Figure 2**, present as candidates for increasing our understanding of these relationships and inform the design and testing of evidence-based dietary interventions to improve mental health.

The Complex Role of Dietary Fiber in Mental Health

Dietary fiber is well recognized for its positive effects on human health, and these benefits are conferred by the physicochemical properties of fiber, such as effects on bowel transit and bile acid metabolism, as well as from its integration within the food matrix, which delivers polyphenols and micronutrients (Puhlmann & de Vos 2022). Specific fiber types can undergo microbial fermentation (e.g., fructo- and galacto-oligosaccharides, resistant starches, pectin, β-glucans) and exert prebiotic effects by serving as substrates for microbial taxa that produce SCFAs, including butyrate. One recent study demonstrated that fiber sources rich in resistant starch strongly predicted fecal butyrate and reduced systemic inflammation with a further modulating effect on the gut microbiome (Oliver et al. 2024), whereas another study showed that a mixed prebiotic fiber blend was shown to reduce inflammation and gastrointestinal symptoms and improve mood in individuals with metabolic syndrome (Hall et al. 2024). Moreover, a mixture of SCFAs has been shown to reduce HPA axis response to a psychosocial stressor in healthy adults (Dalile et al. 2020), an effect that was absent when butyrate alone was administered (Dalile et al. 2024). However, the beneficial effects of fermentable fiber are not universal. Unique host factors, including the gut microbiota composition and functionality, mediate its immunomodulatory effects. For instance, in individuals with inflammatory bowel diseases, poorly degraded β-fructans exacerbate gut inflammation (Armstrong et al. 2023). Similarly, healthy individuals with low baseline SCFA-producer abundance exhibit proinflammatory responses to high-fiber diets (Wastyk et al. 2021), suggesting that insufficient capacity to metabolize fiber can have potentially broad negative effects on

a



b

DIETARY MODIFICATIONS	POSSIBLE BENEFITS
Dietary fiber	Restores SCFAs, improves microbiota composition and function, mood regulation, with metabolic benefits
Antioxidants	Improves cognitive function, reduces ROS, "healthier" microbiota composition and function
Omega-3	Shifts gut microbiota composition and function toward a healthier profile, regulates mood
Nutritional ketosis	Regulates mood, metabolic benefits, reduces ROS levels, improves cognitive function
Fermented foods	Improves cognitive function, restores SCFAs to control levels, regulates mood, metabolic benefits, shifts gut microbiota composition and function toward a healthier profile
Novel functional processed foods	Improves cognitive function, restores SCFAs to control levels, regulates mood, metabolic benefits, shifts gut microbiota composition and function toward a healthier profile, reduces ROS

Figure 2

(*a*) Conceptual representation illustrating the intrinsic relationship between diet and brain function. The left hemisphere of the brain is composed of various fiber- and antioxidant-rich foods, symbolizing the role of dietary components in supporting cognitive and emotional health, whereas the right hemisphere represents the biological structure of the brain, highlighting the importance of nutritional factors. (*b*) Graphical summary of specific dietary components and their potential benefits for brain health and the gut–brain axis. Foods rich in dietary fiber such as fruits and vegetables provide a substrate for the microbes responsible for producing short-chain fatty acids (SCFAs), modulating the gut microbiome, and exerting downstream effects on mood, stress regulation, and metabolic health. Dietary antioxidants, especially found in berries, coffee, and tea, also modulate the gut microbiome and provide benefits for mood and cognitive function and protection from oxidative stress. Dietary fats offer distinct advantages, as omega-3 fatty acids support mood regulation and have prebiotic effects, whereas high-fat, low-carbohydrate diets may enhance mood, improve metabolic outcomes, and potentially reverse cognitive impairments via ketosis and microbiota modulation. Fermented foods, spanning a diverse group including fermented vegetables, dairy products, and beverages, can improve mental health by modulating gut microbiota, providing live microbes, and delivering bioactive compounds. Finally, industrial food processing has the potential to enhance the nutritional quality and benefits of foods, for example, by creating novel functional foods enriched with specific fibers or naturally derived antioxidants. Abbreviation: ROS, reactive oxygen species.

inflammation. Nonetheless, although epidemiological studies report inverse associations between total fiber intake and depressive symptoms, RCTs using isolated fiber supplements mostly show null or inconsistent results (Aslam et al. 2023). This discrepancy suggests that, as opposed to isolated fiber supplements, it is fiber from whole foods, delivered within its food matrix, that may enhance its microbial and host effects. Additionally, it is also possible that long-term dietary habits prime the gut microbiome to positively respond to specific fiber types (Healey et al. 2018).

To summarize, increasing intake of fermentable fiber may support emotional regulation and stress resilience through mechanisms involving SCFA production, HPA axis modulation, and inflammatory response. Fiber-rich foods may also mitigate antipsychotic-induced metabolic disturbances, improving weight control and treatment adherence through their effects on satiety and metabolism (Deehan et al. 2024). However, caution is warranted in individuals receiving stimulant medications, where appetite suppression may be amplified by fiber intake, fostering unintentional weight loss, or, in those with low microbial capacity for fiber fermentation, gastrointestinal discomfort and a proinflammatory response may arise. Consequently, a baseline characterization of the gut microbiome would be an ideal starting point to fine-tune fiber intake.

Antioxidant-Rich Foods and Their Unexplored Potential

Most dietary antioxidants are derived from fruits, vegetables, and beverages such as coffee and tea. Their antioxidant capacity derives from a variety of compounds such as tocopherols, carotenoids, ascorbic acid, and polyphenols. Phenolic compounds are particularly interesting under the lens of the gut–brain axis interactions due to their poor small intestinal absorption, as only 5–10% are absorbed as a monomeric form, thus leaving the majority available for microbial metabolism in the colon (Ross et al. 2024).

In this context, the gut microbiome plays a central role in converting dietary polyphenols into low-molecular-weight bioactive metabolites, which can influence both host physiology and microbial ecology, promoting the growth of beneficial taxa, including *Bifidobacterium* and *Akkermansia*, and butyrate-producing genera, such as *Clostridium* and *Anaerobutyricum* (Lessard-Lord et al. 2024), which may improve gut barrier integrity, reduce inflammation, and potentially exert neuroprotective effects through modulation of the gut–brain axis.

Consistent with these mechanisms, polyphenols can beneficially affect mental health, as diets rich in polyphenols have been linked to improved mood and cognitive function (Lamport & Williams 2020), and meta-analyses indicate that polyphenol supplementation can reduce depressive symptoms, with less reliable effects observed for anxiety and quality of life (Lin et al. 2021). Naturally derived polyphenols prevented depressive- and anxiety-like behaviors in rats subjected to early-life stress, possibly through modulation of the HPA axis, rescue of brain-derived neurotrophic factor levels, and alterations in gut microbiota composition (Donoso et al. 2020). Antioxidant-rich foods are of particular interest for individuals with increased oxidative stress and cognitive dysfunction, such as in ADHD and SSDs. Improved cognitive function due to polyphenol intake could potentially reduce reliance on stimulant medications or mitigate cognitive deficits associated with antipsychotic use. Furthermore, polyphenols may attenuate oxidative stress related to antipsychotic-induced metabolic dysfunction via both direct antioxidant action and microbiome-mediated pathways, although all these applications are speculative and need further research to explore this option. Where increasing antioxidant intake through whole foods is not feasible, polyphenol-rich beverages, such as coffee, tea, green tea, and cocoa, offer a convenient and effective way to deliver antioxidants. Despite these promising findings, however, challenges remain in translating them into interventions, as polyphenols exhibit poor stability and bioavailability when administered as isolated supplements, limiting their therapeutic potential.

Omega-3 Fatty Acids

Omega-3 (n-3) and omega-6 (n-6) polyunsaturated fatty acids (PUFAs) are essential dietary fats involved in immune regulation, cellular signaling, and neurodevelopment. Although n-6 PUFAs are often viewed as proinflammatory, interventional studies show their effects are either neutral or beneficial (Johnson & Fritsche 2012). Additionally, rather than their absolute intake, the n-6:n-3 ratio is often considered as an indicator of inflammatory potential, with low n-3 intake being the main concern (Calder 2018).

Common dietary sources of n-3 fatty acids include alpha-linolenic acid (ALA), found in plant sources such as walnuts and rapeseed oil, and eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), predominantly obtained from oily fish. Although ALA is considered essential, its conversion to EPA and DHA in humans is very limited (Plourde & Cunnane 2007) and most health benefits associated with n-3 fatty acids are attributed to EPA and DHA.

EPA and DHA have demonstrated immunomodulatory and anti-inflammatory properties; thus, their use for improving mental health through alternative means gained considerable interest in psychiatry. Meta-analytic evidence suggests that supplementation with 1–2 g/day of EPA+DHA can reduce depressive symptoms, particularly in individuals with elevated inflammation or low baseline n-3 status (Kelaiditis et al. 2023). However, although depression appears to reliably benefit from n-3 supplementation, no consistent effects have been observed for manic symptoms in BDs (Sarris et al. 2012), psychotic symptoms in SSDs (Montazer et al. 2022), or core symptoms in ADHD (Liu et al. 2023).

Emerging research suggests that n-3 fatty acids modulate the gut microbiota. Preclinical work has demonstrated reduced inflammation and depressive behavior in mice fed a high n-3 diet, and these changes were accompanied by greater fecal *Bifidobacterium* and *Lactobacillus* abundance, which contribute to modulation of immunity, gut permeability, and neurotransmitter synthesis (Robertson et al. 2017). In humans, supplementation with fish oil has been shown to increase the abundance of SCFA-producing taxa such as *Coprococcus* and *Bacteroides* and reduce *Collinsella*, a genus linked to steatohepatitis (Vijay et al. 2021). Another study showed an increased abundance of the SCFA-producing bacteria *Bifidobacterium*, *Roseburia*, and *Lactobacillus* after 12 weeks of n-3 supplementation, although these effects vanished upon washout (Watson et al. 2018). Taken together, these findings suggest a possible prebiotic-like effect of marine n-3 fatty acids, with potential applications to restore SCFA-producing taxa, although it is currently unknown to what extent these microbiota-induced changes explain their anti-inflammatory and immunomodulatory effects.

Ketogenic Diets

On a more macroscopic level, high intakes of dietary fats show promising results in improving mental health, as in the case of the KDs, with limited clinical data suggesting potential benefits of KDs in BDs, major depressive disorder, and SSDs (Dietch et al. 2023). Mechanistically, KDs modulate glutamate and GABA metabolism, support brain energetics through ketone metabolism, and reduce oxidative stress through HDAC inhibition, all of which are implicated in these disorders (Campbell et al. 2025). Additionally, emerging evidence points out unique microbiome-mediated effects of KDs, as they have been shown to downregulate proinflammatory Th17 cells (Ang et al. 2020), a mechanism potentially relevant for conditions such as SSDs in which Th17-related inflammation is implicated (Varun et al. 2019). Although SCFA production may decline on classic KDs due to low fiber intake, a Mediterranean-style KD has been shown to increase *Akkermansia* abundance and fecal butyrate in both healthy and cognitively impaired individuals (Nagpal et al. 2019), supporting the idea that specific dietary modifications of the KD may enhance its therapeutic potential.

Additionally, KDs may improve cognitive function (Chinna-Meyyappan et al. 2023) and mood stability without directly affecting dopaminergic tone, unlike antipsychotic medications (Anderson et al. 2024). This feature is particularly attractive for improving not only positive and negative symptoms of SSDs but also impulsivity, emotional regulation, and cognitive function in ADHD, although specific studies are currently lacking. These features, along with their metabolic benefits (e.g., weight loss, improved insulin sensitivity), make KDs attractive for counteracting metabolic disturbances.

However, KDs are not a panacea and carry significant risks, and they require medical supervision due to risks such as electrolyte imbalance, nephrolithiasis, dyslipidemia, gastrointestinal side effects, and possible interaction with medications (Tagliabue et al. 2024). These issues can be mitigated by increasing the unsaturated:saturated fats ratio or by lowering fat intake and increasing protein intake (e.g., modified Atkins diet) to enhance adherence and reduce adverse effects (Kossoff et al. 2018). Fiber enrichment of KDs, although largely unexplored, may also improve microbiota diversity and mitigate side effects. Preclinical evidence supports increased efficacy of a KD with fiber in a rodent model of epilepsy (Özcan et al. 2025), suggesting a synergistic effect. When a KD is not feasible, safe, or well-tolerated, exogenous ketone or medium-chain triglyceride supplementation can provide a viable alternative to achieve ketosis (Falkenhain et al. 2023). Taken together, carefully designed KDs represent a promising, yet underexplored, avenue for improving mental health outcomes and inflammation and potentially reducing pharmacological burden.

Ultraprocessed Foods: The Janus Face of the Western Diet

Epidemiological studies have consistently linked high UPF consumption with increased risks for obesity, cardiometabolic diseases, and poor mental health (Tessier et al. 2025). These associations have sparked a growing interest in the potential adverse effects of UPFs on the gut microbiota and, therefore, the microbiota–gut–brain axis.

However, a causal relationship between UPFs and health is still largely unexplored. The few available controlled trials do not strongly support an intrinsic deleterious effect of UPFs. For example, in a metabolic ward study, Hall et al. (2019) demonstrated that participants consuming an isocaloric UPF-based diet gained weight compared to those on an unprocessed diet, despite matching macronutrients and fiber content. This effect is readily explained by higher ad libitum food intake driven by greater energy density and palatability of the diet, not necessarily due to intrinsic properties of UPFs. This has been demonstrated by a recent randomized feeding study, in which meals with progressively higher energy density resulted in a progressive increase in energy intake (Lasschuijt et al. 2025). Therefore, these behavioral and contextual factors are good candidates that can account for these observed associations of UPF intake and negative health outcomes.

Links between UPF and the microbiota–gut–brain axis require further experimental validation. An in vitro model of the human colon suggests that certain food additives, such as carrageenan and polysorbate-80, may impair gut barrier integrity and induce low-grade inflammation (Naimi et al. 2021). However, many additives present in UPFs are chemically identical to compounds naturally occurring in whole foods (e.g., citric acid, lecithin, pectin, anthocyanins, carotenoids) with well-known neutral or positive health effects, thus raising doubts about the relevance of these additives in mediating negative health effects of UPFs. Furthermore, commonly employed emulsifiers like soy lecithin and mono-/diglycerides do not exhibit negative effects on gut function and ecology (Naimi et al. 2021).

A further limitation lies in the Nova classification itself, which lacks clarity and reliability and relies on processing level rather than nutritional content, which results in misclassification of nutrient-rich items such as fortified cereals, whole-grain breads, or plant-based meat alternatives as UPFs, despite their potential metabolic benefits (Visioli et al. 2025). Paradoxically, reformulation practices, such as fiber enrichment and micronutrient fortification, can increase a food's Nova category, even when nutritional quality is clearly improved (McClements 2024). Furthermore, processing technologies allow for the incorporation of beneficial ingredients, such as prebiotic fiber blends that selectively promote SCFA-producing taxa and improve intestinal barrier integrity (Cantu-Jungles et al. 2025). Moreover, complexes of phenolic compounds and starches can reduce glycemic load, enhance antioxidant bioavailability, and increase the growth of *Lactobacillus rhamnosus* and *Bifidobacterium bifidum* while inhibiting the growth of *Escherichia coli*, thus conferring prebiotic effects (Cai et al. 2024).

Additionally, UPF-mental health associations may be confounded by social and behavioral variables (Konttinen et al. 2019). Individuals experiencing psychological distress and in difficult life situations may increase their intake of convenient and affordable UPFs, displacing more nutrient-dense foods, making it a problem of nutritional inadequacy rather than an intrinsic negative effect of UPFs. Reverse causality is thus a concern in observational studies, which dominate this field, and, currently, there is no direct evidence linking UPF intake to changes in the gut microbiome that would mediate adverse mental health outcomes. In summary, rather than considering all processed foods harmful, efforts should focus on distinguishing between detrimental and functionally beneficial formulations. A more biologically meaningful classification system, integrating processing characteristics with nutritional, microbial, and metabolic outcomes, is essential for improving our limited understanding of the effects of UPFs on human health. Finally, rigorous, well-controlled randomized trials are needed to disentangle the intrinsic effects of UPFs from other dietary and behavioral factors and to elucidate their direct effect on the gut microbiome (Whelan et al. 2024).

Fermented Foods as Microbial Modulators of Mental Health

Fermented foods are defined as foods made through desired microbial growth and enzymatic conversions of food components involving bacteria, yeasts, or molds (Marco et al. 2021). Common examples include yogurt, kefir, kimchi, and sauerkraut. These foods are increasingly investigated for their effects on human health, including metabolic, gastrointestinal, and even mental health outcomes (Balasubramanian et al. 2024). Observational studies associate fermented food consumption, especially yogurt, with reduced risk of depression (Luo et al. 2023), and intervention studies report a reduction in inflammatory status and increased gut microbiota diversity for a variety of fermented foods (Wastyk et al. 2021).

The health benefits of fermented foods derive from multiple mechanisms. These include the delivery of live microorganisms (e.g., *Lactobacillus*, *Bifidobacterium*) and microbial metabolites such as SCFAs and indole derivatives, increased gut microbial diversity, enhanced micronutrient bioavailability (e.g., B vitamins, vitamin K2), and transformation of polyphenols into more bioavailable forms (Valentino et al. 2024). Fermented foods have also been shown to improve several aspects of brain function relevant for mental health. For example, kefir consumption has improved hippocampal-dependent cognition in humans (Cannavale et al. 2023), and combined interventions using fermented and prebiotic-rich foods in healthy individuals reduced perceived stress, particularly in individuals with resilient microbiota profiles (Berding et al. 2023).

Interestingly, live microbes may not always be necessary to confer benefit. In an RCT, pasteurized sauerkraut improved gut symptoms and was more effective than live variants in increasing fecal SCFA concentrations (Schropp et al. 2025), indicating that prebiotic effects and bacterial components (postbiotics) may be sufficient to produce some of the health benefits.

Fermented foods also offer unique opportunities to improve mental health. Their global availability and cultural adaptability make them suitable for diverse cultural and geographical backgrounds. From a clinical perspective, fermented foods should be evaluated as an option to mitigate antipsychotic-induced metabolic dysfunction and support cognitive function through microbiota-mediated pathways, which could be especially beneficial in ADHD and SSDs. Fermented foods may also potentially rescue a microbiome depleted by psychotropic medication and potentially enhance the response to fiber-based dietary interventions by increasing the abundance of SCFA-producing taxa. These considerations, however, remain speculative.

Despite their multifaceted effects on human health, fermented foods may not always be beneficial, as the fermentation process naturally yields biogenic amines such as histamine, which may cause adverse reactions. Impaired amine degradation capacity, genetics, gut dysbiosis, and medication use contribute to an increased risk of adverse symptoms, including anxiety, headaches, and gastrointestinal distress (Yang et al. 2024). Additionally, the high sodium content of fermented foods may pose risks for individuals sensitive to salt, although it remains unclear whether sodium from fermented sources has the same cardiometabolic impact as sodium from processed foods or if increased sodium intake from fermented foods evens out sodium intake from other sources.

Overall, fermented foods represent a promising but still under-researched tool for supporting gut–brain axis function and mental health. Their effects are modulated by individual microbiota composition, fermentation type, and matrix components. As such, interventions involving fermented foods need personalization, particularly in populations with neuropsychiatric conditions and in individuals sensitive to biogenic amines.

DIET AND THE MICROBIOTA–GUT–BRAIN AXIS: SYNTHESIS AND PERSPECTIVES

Taken together, the evidence suggests that specific dietary components, namely, fiber, antioxidant-rich foods, fermented foods, and dietary fat manipulation through n-3 and ketogenic therapies, may beneficially influence mental health through direct effects and microbiota-mediated mechanisms. Although observational studies provide evidence of diet and mental health relationships, causal evidence from interventional studies is promising but remains underexplored, particularly regarding the involvement of the microbiota–gut–brain axis (for a summary of these studies, see **Table 2**). Nutritional interventions hold the potential as adjunctive strategies in the management of mental health by supporting unmet therapeutic targets such as rescuing cognitive function, reducing reliance on medications, and reducing side effects. The following section discusses current limitations, unexplored options, and future directions necessary to advance the study of diet–microbiome–brain interactions and move the field forward.

DISCUSSION AND FUTURE PERSPECTIVES

Measurement and Inference Challenges in Diet and Mental Health Research

Interpreting diet–gut microbiome relationships requires careful consideration of measurement error. Every dietary assessment method is prone to different types of measurement error and misreporting rates reaching up to 50% compared to the estimated true intake (Bajunaid et al. 2025). The choice of a dietary assessment tool should be based on the research question, timeframe, and target population, as methods (e.g., 24-hour recall, food frequency questionnaires) are not equivalent and they can easily lead to invalid inferences. Similarly, psychometric instruments used to assess mental health outcomes are also subject to measurement error. As these inaccuracies can attenuate observed effects and introduce bias, advanced statistical modeling approaches, including Bayesian and latent variable models (Merkle & Wang 2018), may offer alternative options to deal with these issues, but they still remain underutilized.

The Complexity of Integrating Nutritional Data with the Gut Microbiome

The multidimensionality of nutrition data often precludes the use of the full information provided and instead calls for selecting a smaller set of variables, which is achieved with data reduction techniques or by using dietary indices. Although easily applicable and reproducible, dietary indices have ceiling effects and ignore the contribution of what is not included in the dietary pattern score, and this can be particularly limiting given the compositional nature of dietary data and all the possible interactions between foods and human health (Johnson 2023). Moreover, as dietary indices do not account for the compositional nature of diet, data-driven or a posteriori approaches may be preferable and have been shown to better link diet–gut microbiome composition (Cotillard et al. 2022). An emerging concept, dietary diversity, offers a unique alternative by better capturing nuanced differences in food intake and more meaningfully integrating it with microbiome data (Johnson 2023). Fiber intake may especially benefit from this approach, as not all sources are created equal and different foods provide different types of fiber; hence, simply considering total fiber intake may be too reductive. Additionally, the timing of dietary assessment and stool sampling

Table 2 Overview of interventional studies using diet to modulate the microbiota–gut–brain axis to improve mental health

Population	Type of dietary intervention	Duration	Psychobiological outcomes	Gut microbiota outcomes	Limitations	Reference
45 healthy adults	Psychobiotic diet: high prebiotic fruits/vegetables, whole grains, legumes, fermented foods	4 weeks	↓ Perceived stress in diet group (32% versus 17%), although not significant between groups; higher adherence correlated with reduced stress	↑ *Blautia wexlerae*; ↓ *Blautia obeum*, *Coprococcus comes*, *Dorea longicatena*, *Gemmiger formicilis*, *Eubacteria rectale*, *Bifidobacterium longum*; no change in α/β-diversity	Small sample, short duration, minimal effects on healthy individuals	Berding et al. 2023
24 peri-menopausal women	Plant-based diet + radish seed (5 g/day)	12 weeks	Trend toward improved MoCA and visuospatial/executive function; ↑ ALFF in specific brain areas	↑ Verrucomicrobia, Synergistetes, *Faecalibacterium*; ↓ Firmicutes, Bacteroidetes	No control, small sample, full-diet change limits attribution	Guo et al. 2025
26 healthy adults	Daily inulin-rich vegetables (15 g/day inulin-type fructans)	2 weeks + follow-up	↑ Satiety, ↓ cravings, ↑ emotional competence; no change in perceived stress	↑ *Bifidobacterium*, *Prevotellaceae*, Actinobacteria; ↓ *Alistipes*, *Oscillibacter* Transient changes only	No control, transient microbiota shifts, small sample	Hiel et al. 2019
17 patients with T2DM	High-fiber diet + acarbose versus standard diet + acarbose	8 weeks	↓ Depression/anxiety (HAMD, HAMA)	↑ *Lactobacillus*, *Bifidobacterium*, *Akkermansia*, *Ruminococcus*, *Bacteroides*; ↓ *Desulfovibrio*, *Klebsiella*	Open-label, short duration, acarbose confounding	Chen et al. 2023
60 students	56 g walnuts/day versus no nuts	16 weeks	Walnut group prevented stress-related worsening in mood and stress scores	In females, microbiota diversity maintained ↑ Actinobacteria	Few males, no blinding, pandemic confounding	Herselman et al. 2022
226 older Dutch adults	Plant- versus animal-rich diet (7-day food record)	Cross-sectional	No association with cognitive function	Plant-rich: ↑ *Faecalibacterium prausnitzii*, *E. rectale* Animal-rich: ↑ *Collinsella*, *Streptococcus*, *Ruminococcus gnavus*	Cross-sectional, self-reported diet, ceiling effect on cognition	van Soest et al. 2020
44 Japanese women with obesity	Nutritional education on gut microbiota	8 weeks	↓ Depression (CES-D); ↑ self-rated health	↑ *Bifidobacterium bifidum*, *Streptococcus thermophilus*, *Veillonella parvula*; ↓ *Bacteroides*; ↑ Shannon/Simpson diversity	Generalizability, seasonal/dietary variation, baseline imbalance	Uemura et al. 2019
26 healthy adults	Kefir (25–30 B CFU) versus control dairy (crossover)	4 weeks + washout	↑ Relational memory; no mood/stress change	↑ *Lactobacillus* (esp. *L. zeae*), trend ↑ *Bifidobacterium adolescentis*; ↓ *Phascolarctobacterium*	No link to microbial shift, single-blind	Cannavale et al. 2023
36 healthy women	Fermented milk versus nonfermented milk versus no intervention	4 weeks	↓ Brain reactivity to emotional task (insula, amygdala, PAG); altered resting-state networks	No significant microbial shifts	No mood effects, only women	Tillisch et al. 2013

Abbreviations: ALFF, amplitude of low-frequency fluctuation; CES-D, Center for Epidemiological Studies Depression Scale; HAMA, Hamilton anxiety scale; HAMD, Hamilton depression scale; MoCA, Montreal cognitive assessment; PAG, periaqueductal gray; T2DM, type 2 diabetes mellitus.

is extremely important, as the relationships between diet and the gut microbiota vary depending on whether proximal or habitual dietary intake was assessed, leading to different results (Simm et al. 2025); thus, repeated stool sampling and careful choice of the dietary assessment tool are paramount in minimizing the impact of such potential confounds.

Inconsistent Findings of the Gut Microbiome Across Mental Health

Certain microbial taxa (e.g., *Ruminococcus*, *Prevotella*) are frequently associated with health, but taxonomic classification at the genus level may not be sufficient to correctly interpret findings. For example, although *Ruminococcaceae* are found to be reduced across mental health conditions, studies on ADHD reported inconsistent findings, sometimes with increased *Ruminococcaceae* (Lee et al. 2022). A possible explanation is that although *Ruminococcus bromii* is a known butyrate producer, *Ruminococcus gnavus* lacks this function and it is linked to inflammation (Crost et al. 2023). Similarly, *Prevotella* is often well represented in the gut of healthy individuals, whereas it is depleted in those with several mental health disorders but increased in those with SSDs (Murray et al. 2023). This puzzling evidence may be explained by subtle differences within the taxa, as *Prevotella* can be associated with plant-based diets and metabolic health, but strain-specific forms of *P. copri* can exacerbate inflammation (Abdelsalam et al. 2023). Moreover, some specific microbial signatures within the same mental health condition are not reliably observed between studies, suggesting that differences in the population sampled (e.g., geographic location, medication use), diet, and mental health phenotypes (e.g., depression subtype, comorbidities) may account for such differences (Nikolova et al. 2021). Shared features across mental health disorders, such as emotional dysregulation or cognitive deficits, point toward a transdiagnostic approach to mental health disorders. This is consistent with findings in genetic research on mental health disorders (Bourque et al. 2024), suggesting common underlying biological pathways, and this is paralleled by overlapping microbial signatures. Finally, stool microbial load can significantly affect analytical readouts, further increasing uncertainty in establishing gut microbiome–health associations (Nishijima et al. 2025).

How to Move Diet, Gut Microbiome, and Mental Health Research Forward

Given the complexity of diet, gut microbiome, and brain interactions, a multidisciplinary approach is essential (Diacova et al. 2025, Marx et al. 2024). Dietitians are crucial for dietary intervention design and adherence and in providing expertise in nutritional studies. Similarly, psychologists provide unique expertise in psychometrics, selecting and implementing the most appropriate tools to assess various aspects of mental health and cognitive function, and biostatisticians have a fundamental role in guiding outcome selection, study design, and analysis to maximize efficient resource use given the common constraints of human research. Finally, given the increased interest and demand to improve our food system, food technologists can effectively support functional food design and development (McClements 2024).

From a methodological perspective, increasing reliability of dietary assessment is paramount (Ottaviani et al. 2025), and although biomarkers of food intake can effectively increase accuracy in estimating nutritional intake, the current state of the research is still facing numerous challenges. A growing area of research is focusing on improving dietary assessment methods using advanced machine learning models and food identification through pictures, aiming to overcome human errors and misreporting (Cofre et al. 2025). Gut microbiome analysis would benefit from improved standardization of analytical techniques, bioinformatics pipelines, and sampling from larger and more diverse populations, all of which are necessary advances to establish accurate inferences about microbiome–human health relationships and support impactful research (Joos et al. 2025). Finally, growing evidence supports a paradigm shift in mental health care and research looking at a broader, integrated perspective and the need to update symptomatology measurements by including outcomes that matter to the patients (Veal et al. 2024).

Traditionally, although RCTs are considered the gold standard for inferring causality, they often face limitations such as smaller than planned sample sizes, challenges in blinding, the placebo effect, and inadequate exposure to a dietary intervention (Ludwig et al. 2025), all contributing to inconsistencies in their findings. Observational research is often only seen as just a mere association between variables, but when properly designed and executed, it can provide support for causal relationships (Igelström et al. 2022), thus providing valuable and complementary evidence to interventional research. For instance, formal tools such as directed acyclic graphs help clarify

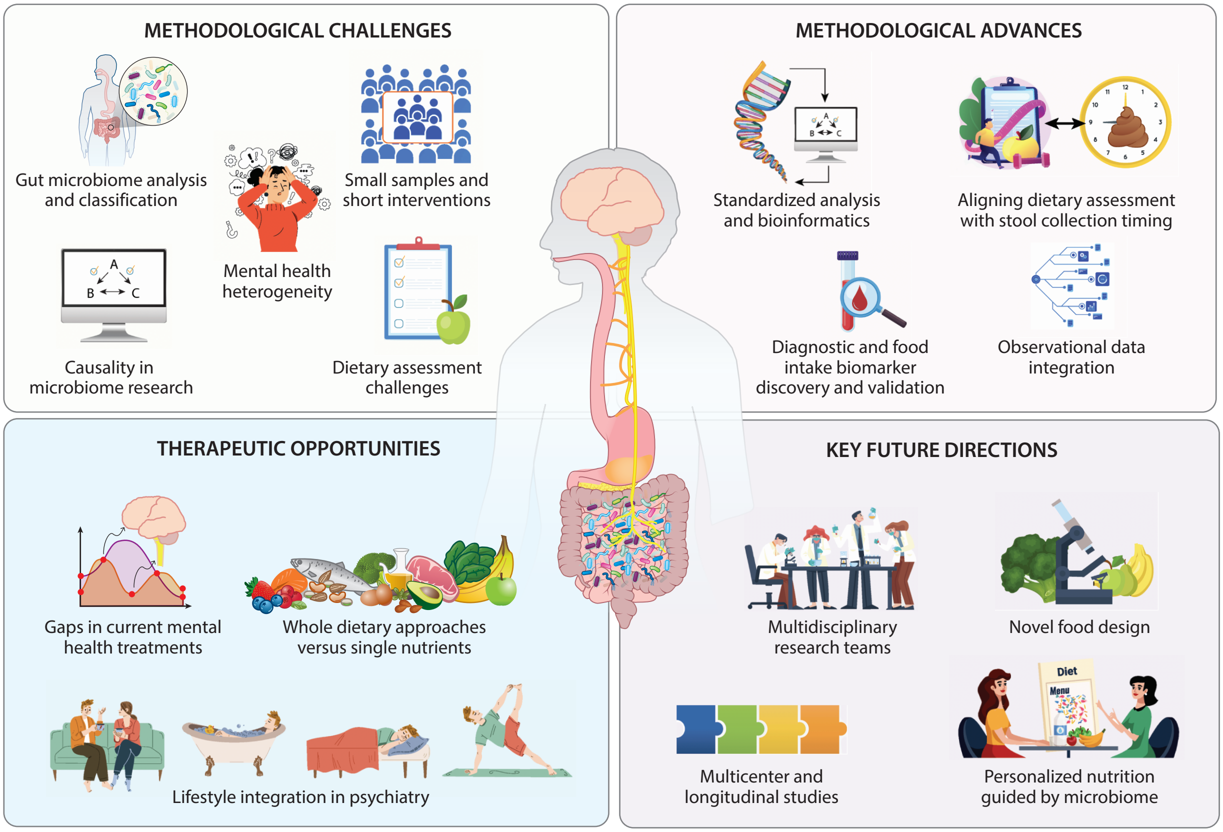


Figure 3

Overview of methodological challenges, advances, therapeutic opportunities, and future directions in the study of diet, the gut microbiome, and brain health. Top left: Methodological challenges include heterogeneity in gut microbiome analysis, small sample sizes and short intervention durations, heterogeneity in mental health disorders and outcomes, and dietary assessment difficulties, which all contribute to current challenges in establishing causality in the gut microbiome field. Top right: Methodological advances such as standardized analysis pipelines, biomarker discovery, improved dietary assessment tools aligned with stool collection timing, and integration of complementary evidence from large-scale observational data are needed to help address current limitations. Bottom left: Therapeutic opportunities in mental health care include filling the gaps in mental health treatment, providing alternative or complementary therapies such as diet and other lifestyle-based strategies in psychiatric care, and emphasizing whole-diet approaches. Bottom right: Key future directions highlight the importance of multidisciplinary research teams, novel food design to improve the nutritional profile of foods, multicenter and longitudinal studies to increase statistical power, and the development of personalized nutrition strategies informed by gut microbiome profiles.

assumptions and relationships between variables and identify potential sources of bias, especially when combined with longitudinal data and appropriate modeling strategies.

In conclusion, although extensive evidence links food and mental health, diet and the gut microbiome, or mental health and the gut microbiome, very little research integrates these three closely related aspects of human health. At the current stage, many questions surrounding the research on food, the gut microbiome, and mental health still need to be answered. This field now needs robust, reproducible evidence, improved analytical techniques, more robust methodology, and interdisciplinary collaboration (for a summary, see **Figure 3**).

This research area holds promise for addressing gaps in mental health care, as dietary interventions may offer an accessible and cost-effective strategy (Chatterton et al. 2018), especially for selected individuals who face barriers to conventional treatments such as psychotherapy or pharmacotherapy due to costs, availability, and waiting times. As gut microbiome research keeps steadily advancing, it offers new perspectives on and insights into the intricate relationship between diet and mental health and is paving the way for personalized/precision nutritional approaches to improve mental health.

DISCLOSURE STATEMENT

A.F. and L.T.P. are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review. E.S. has received an honorarium from Janssen Sciences Ireland UC. E.S. also received an honorarium from MyNutriWeb for an event that was sponsored by Yakult. G.C. has received honoraria from Janssen, Probi, Apsen, and Ingelheim Boehringer as an invited speaker; is in receipt of research funding from Pharmavite, Fonterra, Reckitt, Nestle, and Tate and Lyle; and has been paid for consultancy work by Yakult, Zentiva, Bayer Healthcare, and Heel Pharmaceuticals. J.F.C. has been an invited speaker at conferences organized by Bromotech, Yakult, Nutricia, and Nestle and has received research funding from Kerry Foods, DuPont/IFF, and Nestle.

ACKNOWLEDGMENTS

The authors thank Dr. Ken O'Riordan for his support in creating the figures used in this review.

LITERATURE CITED

Abdelsalam NA, Hegazy SM, Aziz RK. 2023. The curious case of *Prevotella copri*. *Gut Microbes* 15:2249152

Aburto MR, Cryan JF. 2024. Gastrointestinal and brain barriers: unlocking gates of communication across the microbiota-gut-brain axis. *Nat. Rev. Gastroenterol. Hepatol.* 21:222–47

Agorastos A, Heinig A, Stiedl O, Hager T, Sommer A, et al. 2019. Vagal effects of endocrine HPA axis challenges on resting autonomic activity assessed by heart rate variability measures in healthy humans. *Psychoneuroendocrinology* 102:196–203

American Psychiatric Association. 2022. *Diagnostic and Statistical Manual of Mental Disorders*, *DSM-5-TR*. American Psychiatric Association Publishing

Anderson J, Ozan E, Chouinard V-A, Grant G, MacDonald A, et al. 2024. The ketogenic diet as a transdiagnostic treatment for neuropsychiatric disorders: mechanisms and clinical outcomes. *Curr. Treat. Options Psych.* 12:1

Ang QY, Alexander M, Newman JC, Tian Y, Cai J, et al. 2020. Ketogenic diets alter the gut microbiome resulting in decreased intestinal Th17 cells. *Cell* 181:1263–75.e16

Armstrong HK, Bording-Jorgensen M, Santer DM, Zhang Z, Valcheva R, et al. 2023. Unfermented β-fructan fibers fuel inflammation in select inflammatory bowel disease patients. *Gastroenterology* 164:228–40

Ashton MM, Dean OM, Marx W, Mohebbi M, Berk M, et al. 2020. Diet quality, dietary inflammatory index and body mass index as predictors of response to adjunctive *N*-acetylcysteine and mitochondrial agents in adults with bipolar disorder: a sub-study of a randomised placebo-controlled trial. *Aust. N. Z. J. Psychiatry* 54:159–72

Aslam F, Lotfalian M, So D, Berding K, Berk M, et al. 2023. Fiber intake and fiber intervention in depression and anxiety: a systematic review and meta-analysis of observational studies and randomized controlled trials. *Nutr. Rev.* 82(12):1678–95

Asnicar F, Berry SE, Valdes AM, Nguyen LH, Piccinno G, et al. 2021. Microbiome connections with host metabolism and habitual diet from 1,098 deeply phenotyped individuals. *Nat. Med.* 27:321–32

Azzam A. 2021. Is the world converging to a 'Western diet'? *Public Health Nutr.* 24:309–17

Bajunaid R, Niu C, Hambly C, Liu Z, Yamada Y, et al. 2025. Predictive equation derived from 6,497 doubly labelled water measurements enables the detection of erroneous self-reported energy intake. *Nat. Food* 6:58–71

Balasubramanian R, Schneider E, Gunnigle E, Cotter PD, Cryan JF. 2024. Fermented foods: harnessing their potential to modulate the microbiota-gut-brain axis for mental health. *Neurosci. Biobehav. Rev.* 158:105562

Barrea L, Verde L, Vetrani C, Marino F, Aprano S, et al. 2022. VLCKD: a real time safety study in obesity. *J. Transl. Med.* 20:23

Bayes J, Schloss J, Sibbritt D. 2022. The effect of a Mediterranean diet on the symptoms of depression in young males (the "AMMEND: A Mediterranean Diet in MEN with Depression" study): a randomized controlled trial. *Am. J. Clin. Nutr.* 116:572–80

Berding K, Bastiaanssen TFS, Moloney GM, Boscaini S, Strain CR, et al. 2023. Feed your microbes to deal with stress: a psychobiotic diet impacts microbial stability and perceived stress in a healthy adult population. *Mol. Psychiatry* 28:601–10

Bourque V-R, Poulain C, Proulx C, Moreau CA, Joober R, et al. 2024. Genetic and phenotypic similarity across major psychiatric disorders: a systematic review and quantitative assessment. *Transl. Psychiatry* 14:171

Bravo JA, Forsythe P, Chew MV, Escaravage E, Savignac HM, et al. 2011. Ingestion of *Lactobacillus* strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. *PNAS* 108:16050–55

Brum M, Nieberler M, Kehrwald C, Knopf K, Brunkhorst-Kanaan N, et al. 2023. Phase- and disorder-specific differences in peripheral metabolites of the kynurenine pathway in major depression, bipolar affective disorder and schizophrenia. *World J. Biol. Psychiatry* 24:564–77

Butler MI, Kittel-Schneider S, Wagner-Skacel J, Mörkl S, Clarke G. 2025. The gut microbiome in anxiety disorders. *Curr. Psychiatry Rep.* 27:347–61

Cai M, Feng J, Wang J, Chen P, Ge Z, et al. 2024. Characterization of various noncovalent polyphenol-starch complexes and their prebiotic activities during in vitro digestion and fermentation. *J. Agric. Food Chem.* 72:2250–62

Calder PC. 2018. Very long-chain *n*-3 fatty acids and human health: fact, fiction and the future. *Proc. Nutr. Soc.* 77:52–72

Campbell IH, Needham N, Grossi H, Kamenska I, Luz S, et al. 2025. A pilot study of a ketogenic diet in bipolar disorder: clinical, metabolic and magnetic resonance spectroscopy findings. *BJPsych Open* 11:e34

Cannavale CN, Mysonhimer AR, Bailey MA, Cohen NJ, Holscher HD, Khan NA. 2023. Consumption of a fermented dairy beverage improves hippocampal-dependent relational memory in a randomized, controlled cross-over trial. *Nutr. Neurosci.* 26:265–74

Cantu-Jungles TM, Agamennone V, Van Den Broek TJ, Schuren FHJ, Hamaker B. 2025. Systematically-designed mixtures outperform single fibers for gut microbiota support. *Gut Microbes* 17:2442521

Chang JP-C, Su K-P, Mondelli V, Pariante CM. 2021. Cortisol and inflammatory biomarker levels in youths with attention deficit hyperactivity disorder (ADHD): evidence from a systematic review with meta-analysis. *Transl. Psychiatry* 11:430

Chatterton ML, Mihalopoulos C, O'Neil A, Itsiopoulos C, Opie R, et al. 2018. Economic evaluation of a dietary intervention for adults with major depression (the "SMILES" trial). *BMC Public Health* 18:599

Chen L, Liu B, Ren L, Du H, Fei C, et al. 2023. High-fiber diet ameliorates gut microbiota, serum metabolism and emotional mood in type 2 diabetes patients. *Front. Cell. Infect. Microbiol.* 13:1069954

Chinna-Meyyappan A, Gomes FA, Koning E, Fabe J, Breda V, Brietzke E. 2023. Effects of the ketogenic diet on cognition: a systematic review. *Nutr. Neurosci.* 26:1258–78

Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, et al. 2018. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *Lancet* 391:1357–66

Cofre S, Sanchez C, Quezada-Figueroa G, López-Cortés XA. 2025. Validity and accuracy of artificial intelligence-based dietary intake assessment methods: a systematic review. *Br. J. Nutr.* 133(9):1241–53

Cotillard A, Cartier-Meheust A, Litwin NS, Chaumont S, Saccareau M, et al. 2022. A posteriori dietary patterns better explain variations of the gut microbiome than individual markers in the American Gut Project. *Am. J. Clin. Nutr.* 115:432–43

Crost EH, Coletto E, Bell A, Juge N. 2023. *Ruminococcus gnavus*: friend or foe for human health. *FEMS Microbiol. Rev.* 47:fuad014

Cryan JF, Dinan TG. 2012. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. *Nat. Rev. Neurosci.* 13:701–12

Cryan JF, O'Riordan KJ, Cowan CSM, Sandhu KV, Bastiaanssen TFS, et al. 2019. The microbiota-gut-brain axis. *Physiol. Rev.* 99:1877–2013

Cussotto S, Sandhu KV, Dinan TG, Cryan JF. 2018. The neuroendocrinology of the microbiota-gut-brain axis: a behavioural perspective. *Front. Neuroendocrinol.* 51:80–101

Dalile B, Fuchs A, La Torre D, Vervliet B, Van Oudenhove L, Verbeke K. 2024. Colonic butyrate administration modulates fear memory but not the acute stress response in men: a randomized, triple-blind, placebo-controlled trial. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* 131:110939

Dalile B, Vervliet B, Bergonzelli G, Verbeke K, Van Oudenhove L. 2020. Colon-delivered short-chain fatty acids attenuate the cortisol response to psychosocial stress in healthy men: a randomized, placebo-controlled trial. *Neuropsychopharmacology* 45:2257–66

Deehan EC, Mocanu V, Madsen KL. 2024. Effects of dietary fibre on metabolic health and obesity. *Nat. Rev. Gastroenterol. Hepatol.* 21:301–18

Di Polito N, Stylianakis AA, Richardson R, Baker KD. 2023. Real-world intake of dietary sugars is associated with reduced cortisol reactivity following an acute physiological stressor. *Nutrients* 15:209

Diacova T, Cifelli CJ, Davis CD, Holscher HD, Kable ME, et al. 2025. Best practices and considerations for conducting research on diet–gut microbiome interactions and their impact on health in adult populations: an umbrella review. *Adv. Nutr.* 16:100419

Dicken SJ, Batterham RL. 2024. Ultra-processed food and obesity: What is the evidence? *Curr. Nutr. Rep.* 13:23–38

Dietch DM, Kerr-Gaffney J, Hockey M, Marx W, Ruusunen A, et al. 2023. Efficacy of low carbohydrate and ketogenic diets in treating mood and anxiety disorders: systematic review and implications for clinical practice. *BJPsych Open* 9:e70

Dilmore AH, Kuplicki R, McDonald D, Kumar M, Estaki M, et al. 2025. Medication use is associated with distinct microbial features in anxiety and depression. *Mol. Psychiatry* 30:2545–57

Dong TS, Luu K, Lagishetty V, Sedighian F, Woo S-L, et al. 2020. A high protein calorie restriction diet alters the gut microbiome in obesity. *Nutrients* 12:3221

Donoso F, Egerton S, Bastiaanssen TFS, Fitzgerald P, Gite S, et al. 2020. Polyphenols selectively reverse early-life stress-induced behavioural, neurochemical and microbiota changes in the rat. *Psychoneuroendocrinology* 116:104673

Evans SJ, Bassis CM, Hein R, Assari S, Flowers SA, et al. 2017. The gut microbiome composition associates with bipolar disorder and illness severity. *J. Psychiatr. Res.* 87:23–29

Fackelmann G, Manghi P, Carlino N, Heidrich V, Piccinno G, et al. 2025. Gut microbiome signatures of vegan, vegetarian and omnivore diets and associated health outcomes across 21,561 individuals. *Nat. Microbiol.* 10:41–52

Falkenhain K, Islam H, Little JP. 2023. Exogenous ketone supplementation: an emerging tool for physiologists with potential as a metabolic therapy. *Exp. Physiol.* 108:177–87

Fu Y, Chen S-J, Wang Z-B, Zhang D-D, Gao P-Y, et al. 2025. Dietary inflammatory index and brain disorders: a large prospective cohort study. *Transl. Psychiatry* 15:99

Fülling C, Dinan TG, Cryan JF. 2019. Gut microbe to brain signaling: what happens in vagus.... *Neuron* 101:998–1002

GBD 2019 Mental Disorders Collaborators. 2022. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Psychiatry* 9:137–50

Gheorghe CE, Martin JA, Manriquez FV, Dinan TG, Cryan JF, Clarke G. 2019. Focus on the essentials: tryptophan metabolism and the microbiome-gut-brain axis. *Curr. Opin. Pharmacol.* 48:137–45

Godos J, Bonaccio M, Al-Qahtani WH, Marx W, Lane MM, et al. 2023. Ultra-processed food consumption and depressive symptoms in a Mediterranean cohort. *Nutrients* 15:504

Goldsmith DR, Rapaport MH, Miller BJ. 2016. A meta-analysis of blood cytokine network alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder and depression. *Mol. Psychiatry* 21:1696–709

Gong X, Cai Q, Liu X, An D, Zhou D, et al. 2021. Gut flora and metabolism are altered in epilepsy and partially restored after ketogenic diets. *Microb. Pathog.* 155:104899

Guasch-Ferré M, Willett WC. 2021. The Mediterranean diet and health: a comprehensive overview. *J. Intern. Med.* 290:549–66

Guo C, Xiong Z, Yang L, Bai M, Zhu Y, Zeng X. 2025. Effects of a healthy diet based on seed-rich vegetables on the gut microbiota and intrinsic brain activity in perimenopausal women: a pilot study on cognitive improvement. *Sci. Rep.* 15:17444

Hall CV, Hepsomali P, Dalile B, Scapozza L, Gurry T. 2024. Effects of a diverse prebiotic fibre blend on inflammation, the gut microbiota and affective symptoms in metabolic syndrome: a pilot open-label randomised controlled trial. *Br. J. Nutr.* 132:1002–13

Hall KD, Ayuketah A, Brychta R, Cai H, Cassimatis T, et al. 2019. Ultra-processed diets cause excess calorie intake and weight gain: an inpatient randomized controlled trial of ad libitum food intake. *Cell Metab.* 30:67–77.e3

Hareer LW, Lau YY, Mole F, Reidlinger DP, O'Neill HM, et al. 2025. The effectiveness of the Mediterranean diet for primary and secondary prevention of cardiovascular disease: an umbrella review. *Nutr. Diet.* 82:8–41

Healey G, Murphy R, Butts C, Brough L, Whelan K, Coad J. 2018. Habitual dietary fibre intake influences gut microbiota response to an inulin-type fructan prebiotic: a randomised, double-blind, placebo-controlled, cross-over, human intervention study. *Br. J. Nutr.* 119:176–89

Herselman MF, Bailey S, Deo P, Zhou X-F, Gunn KM, Bobrovskaya L. 2022. The effects of walnuts and academic stress on mental health, general well-being and the gut microbiota in a sample of university students: a randomised clinical trial. *Nutrients* 14:4776

Hiel S, Bindels LB, Pachikian BD, Kalala G, Broers V, et al. 2019. Effects of a diet based on inulin-rich vegetables on gut health and nutritional behavior in healthy humans. *Am. J. Clin. Nutr.* 109:1683–95

Hung LY, Alves ND, Del Colle A, Talati A, Najjar SA, et al. 2025. Intestinal epithelial serotonin as a novel target for treating disorders of gut-brain interaction and mood. *Gastroenterology* 168:754–68

Igelström E, Craig P, Lewsey J, Lynch J, Pearce A, Katikireddi SV. 2022. Causal inference and effect estimation using observational data. *J. Epidemiol. Commun. Health* 76:960–66

Jacka FN. 2017. Nutritional psychiatry: Where to next? *EBioMedicine* 17:24–29

Jacka FN, O'Neil A, Opie R, Itsiopoulos C, Cotton S, et al. 2017. A randomised controlled trial of dietary improvement for adults with major depression (the 'SMILES' trial). *BMC Med.* 15:23

Jäger R, Kerksick CM, Campbell BI, Cribb PJ, Wells SD, et al. 2017. International Society of Sports Nutrition position stand: protein and exercise. *J. Int. Soc. Sports Nutr.* 14:20

Johnson AJ. 2023. Connecting the healthy eating index with microbiota diversity. *J. Nutr.* 153:1846–47

Johnson GH, Fritsche K. 2012. Effect of dietary linoleic acid on markers of inflammation in healthy persons: a systematic review of randomized controlled trials. *J. Acad. Nutr. Diet.* 112:1029–41.e15

Joos R, Boucher K, Lavelle A, Arumugam M, Blaser MJ, et al. 2025. Examining the healthy human microbiome concept. *Nat. Rev. Microbiol.* 23:192–205

Jung B, Yang C, Lee S-H. 2024. Vagus nerves stimulation: clinical implication and practical issue as a neuropsychiatric treatment. *Clin. Psychopharmacol. Neurosci.* 22:13–22

Kelaiditis CF, Gibson EL, Dyall SC. 2023. Effects of long-chain omega-3 polyunsaturated fatty acids on reducing anxiety and/or depression in adults; a systematic review and meta-analysis of randomised controlled trials. *Prostaglandins Leukot. Essent. Fatty Acids* 192:102572

Kelly JR, Clarke G, Cryan JF, Dinan TG. 2018. Dimensional thinking in psychiatry in the era of the Research Domain Criteria (RDoC). *Ir. J. Psychol. Med.* 35:89–94

Kennedy PJ, Cryan JF, Dinan TG, Clarke G. 2017. Kynurenine pathway metabolism and the microbiota-gut-brain axis. *Neuropharmacology* 112:399–412

Konttinen H, Van Strien T, Männistö S, Jousilahti P, Haukkala A. 2019. Depression, emotional eating and long-term weight changes: a population-based prospective study. *Int. J. Behav. Nutr. Phys. Act.* 16:28

Kossoff EH, Zupec-Kania BA, Auvin S, Ballaban-Gil KR, Christina Bergqvist AG, et al. 2018. Optimal clinical management of children receiving dietary therapies for epilepsy: updated recommendations of the International Ketogenic Diet Study Group. *Epilepsia Open* 3:175–92

Lamport DJ, Williams CM. 2020. Polyphenols and cognition in humans: an overview of current evidence from recent systematic reviews and meta-analyses. *Brain Plast.* 6:139–53

Lane MM, Travica N, Gamage E, Marshall S, Trakman GL, et al. 2024. Sugar-sweetened beverages and adverse human health outcomes: an umbrella review of meta-analyses of observational studies. *Annu. Rev. Nutr.* 44:383–404

Lasschuijt MP, Heuven LA, Gonzalez-Estanol K, Siebelink E, Chen Y, Forde CG. 2025. The effect of energy density and eating rate on ad libitum energy intake in healthy adults—a randomized controlled study. *J. Nutr.* 155(8):2602–10

Lee M, Ball L, Hill S, Crowe TC, Walsh H, et al. 2025. Omnivore, vegan and vegetarian diet quality associations with depressive symptoms: a comparative cross-sectional analysis of the Australian Longitudinal Study on Women's Health. *J. Affect. Disord.* 370:18–25

Lee M-J, Lai H-C, Kuo Y-L, Chen VC-H. 2022. Association between gut microbiota and emotional-behavioral symptoms in children with attention-deficit/hyperactivity disorder. *J. Pers. Med.* 12:1634

Lessard-Lord J, Roussel C, Lupien-Meilleur J, Généreux P, Richard V, et al. 2024. Short term supplementation with cranberry extract modulates gut microbiota in human and displays a bifidogenic effect. *npj Biofilms Microbiomes* 10:18

Lin K, Li Y, Toit ED, Wendt L, Sun J. 2021. Effects of polyphenol supplementations on improving depression, anxiety, and quality of life in patients with depression. *Front. Psychiatry* 12:765485

Liu T-H, Wu J-Y, Huang P-Y, Lai C-C, Chang JP-C, et al. 2023. Omega-3 polyunsaturated fatty acids for core symptoms of attention-deficit/hyperactivity disorder: a meta-analysis of randomized controlled trials. *J. Clin. Psychiatry* 84(5):22r14772

Liu WW, Reicher N, Alway E, Rupprecht LE, Weng P, et al. 2025. A gut sense for a microbial pattern regulates feeding. *Nature* 645:729–36

Ludwig DS, Willett WC, Putt ME. 2025. Wash-in and washout effects: mitigating bias in short term dietary and other trials. *BMJ* 389:e082963

Lum GR, Ha SM, Olson CA, Blencowe M, Paramo J, et al. 2023. Ketogenic diet therapy for pediatric epilepsy is associated with alterations in the human gut microbiome that confer seizure resistance in mice. *Cell Rep.* 42:113521

Luo Y, Li Z, Gu L, Zhang K. 2023. Fermented dairy foods consumption and depressive symptoms: a meta-analysis of cohort studies. *PLOS ONE* 18:e0281346

Marco ML, Sanders ME, Gänzle M, Arrieta MC, Cotter PD, et al. 2021. The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on fermented foods. *Nat. Rev. Gastroenterol. Hepatol.* 18:196–208

Marx W, Visser M, Wallace C, Jacka FN, Bayes J, et al. 2024. Methodological and reporting recommendations for clinical trials in Nutritional Psychiatry: guidelines from the International Society for Nutritional Psychiatry Research. *Br. J. Nutr.* **https://doi.org/10.1017/S0007114524001946**

Matison AP, Mather KA, Flood VM, Reppermund S. 2021. Associations between nutrition and the incidence of depression in middle-aged and older adults: a systematic review and meta-analysis of prospective observational population-based studies. *Ageing Res. Rev.* 70:101403

McClements DJ. 2024. Designing healthier and more sustainable ultraprocessed foods. *Comp. Rev. Food Sci. Food Saf.* 23:e13331

McGuinness AJ, Davis JA, Dawson SL, Loughman A, Collier F, et al. 2022. A systematic review of gut microbiota composition in observational studies of major depressive disorder, bipolar disorder and schizophrenia. *Mol. Psychiatry* 27:1920–35

Merkle EC, Wang T. 2018. Bayesian latent variable models for the analysis of experimental psychology data. *Psychon. Bull. Rev.* 25:256–70

Mohr AE, Jäger R, Carpenter KC, Kerksick CM, Purpura M, et al. 2020. The athletic gut microbiota. *J. Int. Soc. Sports Nutr.* 17:24

Montazer M, Ebrahimpour-Koujan S, Surkan PJ, Azadbakht L. 2022. Effects of fish-oil consumption on psychological function outcomes in psychosis: a systematic review and dose-response meta-analysis of randomized controlled trials. *Adv. Nutr.* 13:2149–64

Monteiro CA, Cannon G, Levy RB, Moubarac J-C, Louzada ML, et al. 2019. Ultra-processed foods: what they are and how to identify them. *Public Health Nutr.* 22:936–41

Murray N, Al Khalaf S, Bastiaanssen TFS, Kaulmann D, Lonergan E, et al. 2023. Compositional and functional alterations in intestinal microbiota in patients with psychosis or schizophrenia: a systematic review and meta-analysis. *Schizophr. Bull.* 49:1239–55

Nagpal R, Neth BJ, Wang S, Craft S, Yadav H. 2019. Modified Mediterranean-ketogenic diet modulates gut microbiome and short-chain fatty acids in association with Alzheimer's disease markers in subjects with mild cognitive impairment. *EBioMedicine* 47:529–42

Naimi S, Viennois E, Gewirtz AT, Chassaing B. 2021. Direct impact of commonly used dietary emulsifiers on human gut microbiota. *Microbiome* 9:66

Nikolova VL, Smith MRB, Hall LJ, Cleare AJ, Stone JM, Young AH. 2021. Perturbations in gut microbiota composition in psychiatric disorders: a review and meta-analysis. *JAMA Psychiatry* 78:1343

Nishijima S, Stankevic E, Aasmets O, Schmidt TSB, Nagata N, et al. 2025. Fecal microbial load is a major determinant of gut microbiome variation and a confounder for disease associations. *Cell* 188:222–36.e15

Ogden CL, Ansai N, Fryar CD, Wambogo EA, Brody DJ. 2025. Depression and diet quality, US adolescents and young adults: National Health and Nutrition Examination Survey, 2015–March 2020. *J. Acad. Nutr. Diet.* 125:247–55

Oliver A, Alkan Z, Stephensen CB, Newman JW, Kable ME, Lemay DG. 2024. Diet, microbiome, and inflammation predictors of fecal and plasma short-chain fatty acids in humans. *J. Nutr.* 154:3298–311

Olson CA, Vuong HE, Yano JM, Liang QY, Nusbaum DJ, Hsiao EY. 2018. The gut microbiota mediates the anti-seizure effects of the ketogenic diet. *Cell* 173:1728–41.e13

O'Neil A, Perez J, Young LM, John T, Turner M, et al. 2024. Clinical and cost-effectiveness of remote-delivered, online lifestyle therapy versus psychotherapy for reducing depression: results from the CALM non-inferiority, randomised trial. *Lancet Reg. Health West. Pac.* 49:101142

O'Riordan KJ, Moloney GM, Keane L, Clarke G, Cryan JF. 2025. The gut microbiota-immune-brain axis: therapeutic implications. *Cell Rep. Med.* 6:101982

Ottaviani JI, Schroeter H, Bier DM, Erdman JW, Sesso HD, et al. 2025. The overlooked impact of background diet and adherence in nutrition trials. *Food Funct.* 16(14):5733–43

Özcan E, Yu KB, Dinh L, Lum GR, Lau K, et al. 2025. Dietary fiber content in clinical ketogenic diets modifies the gut microbiome and seizure resistance in mice. *Nat. Commun.* 16:987

Plourde M, Cunnane SC. 2007. Extremely limited synthesis of long chain polyunsaturates in adults: implications for their dietary essentiality and use as supplements. *Appl. Physiol. Nutr. Metab.* 32:619–34

Puhlmann M-L, de Vos WM. 2022. Intrinsic dietary fibers and the gut microbiome: rediscovering the benefits of the plant cell matrix for human health. *Front. Immunol.* 13:954845

Quidé Y, Girshkin L, Watkeys OJ, Carr VJ, Green MJ. 2021. The relationship between cortisol reactivity and emotional brain function is differently moderated by childhood trauma, in bipolar disorder, schizophrenia and healthy individuals. *Eur. Arch. Psychiatry Clin. Neurosci.* 271:1089–110

Raz O, Steinvil A, Berliner S, Rosenzweig T, Justo D, Shapira I. 2013. The effect of two iso-caloric meals containing equal amounts of fats with a different fat composition on the inflammatory and metabolic markers in apparently healthy volunteers. *J. Inflamm.* 10:3

Ribeiro G, Ferri A, Clarke G, Cryan JF. 2022. Diet and the microbiota–gut–brain-axis: a primer for clinical nutrition. *Curr. Opin. Clin. Nutr. Metab. Care* 25:443–50

Robertson RC, Seira Oriach C, Murphy K, Moloney GM, Cryan JF, et al. 2017. Omega-3 polyunsaturated fatty acids critically regulate behaviour and gut microbiota development in adolescence and adulthood. *Brain Behav. Immun.* 59:21–37

Ross FC, Patangia D, Grimaud G, Lavelle A, Dempsey EM, et al. 2024. The interplay between diet and the gut microbiome: implications for health and disease. *Nat. Rev. Microbiol.* 22:671–86

Sanz Y, Cryan JF, Deschasaux-Tanguy M, Elinav E, Lambrecht R, Veiga P. 2025. The gut microbiome connects nutrition and human health. *Nat. Rev. Gastroenterol. Hepatol.* 22:534–55

Sarris J, Mischoulon D, Schweitzer I. 2012. Omega-3 for bipolar disorder: meta-analyses of use in mania and bipolar depression. *J. Clin. Psychiatry* 73:81–86

Schropp N, Bauer A, Stanislas V, Huang KD, Lesker T-R, et al. 2025. The impact of regular sauerkraut consumption on the human gut microbiota: a crossover intervention trial. *Microbiome* 13:52

Sen T, Cawthon CR, Ihde BT, Hajnal A, DiLorenzo PM, et al. 2017. Diet-driven microbiota dysbiosis is associated with vagal remodeling and obesity. *Physiol. Behav.* 173:305–17

Shareghfarid E, Sangsefidi ZS, Salehi-Abargouei A, Hosseinzadeh M. 2020. Empirically derived dietary patterns and food groups intake in relation with attention deficit/hyperactivity disorder (ADHD): a systematic review and meta-analysis. *Clin. Nutr. ESPEN* 36:28–35

Simm NM, Hoedt EC, Caban SJ, Tooley KL, Peterson R, et al. 2025. Differences in diet-microbiome associations dependent on dietary collection methods for proximal and habitual dietary intake. *Proc. Nutr. Soc.* 84:E16

Solmi M, Radua J, Olivola M, Croce E, Soardo L, et al. 2022. Age at onset of mental disorders worldwide: large-scale meta-analysis of 192 epidemiological studies. *Mol. Psychiatry* 27:281–95

Sonnenburg ED, Sonnenburg JL. 2014. Starving our microbial self: the deleterious consequences of a diet deficient in microbiota-accessible carbohydrates. *Cell Metab.* 20:779–86

Stiernborg M, Debelius J, Yang LL, Skott E, Millischer V, et al. 2023. Bacterial gut microbiome differences in adults with ADHD and in children with ADHD on psychostimulant medication. *Brain Behav. Immunity* 110:310–21

Sudo N, Chida Y, Aiba Y, Sonoda J, Oyama N, et al. 2004. Postnatal microbial colonization programs the hypothalamic-pituitary-adrenal system for stress response in mice. *J. Physiol.* 558:263–75

Tagliabue A, Armeno M, Berk KA, Guglielmetti M, Ferraris C, et al. 2024. Ketogenic diet for epilepsy and obesity: Is it the same? *Nutr. Metab. Cardiovasc. Dis.* 34:581–89

Tessier A-J, Wang F, Korat AA, Eliassen AH, Chavarro J, et al. 2025. Optimal dietary patterns for healthy aging. *Nat. Med.* 31:1644–52

Tillisch K, Labus J, Kilpatrick L, Jiang Z, Stains J, et al. 2013. Consumption of fermented milk product with probiotic modulates brain activity. *Gastroenterology* 144:1394–401.e4

Tofani GSS, Leigh S-J, Gheorghe CE, Bastiaanssen TFS, Wilmes L, et al. 2025. Gut microbiota regulates stress responsivity via the circadian system. *Cell Metab.* 37:138–53.e5

Trefflich I, Jabakhanji A, Menzel J, Blaut M, Michalsen A, et al. 2020. Is a vegan or a vegetarian diet associated with the microbiota composition in the gut? Results of a new cross-sectional study and systematic review. *Crit. Rev. Food Sci. Nutr.* 60:2990–3004

Uemura M, Hayashi F, Ishioka K, Ihara K, Yasuda K, et al. 2019. Obesity and mental health improvement following nutritional education focusing on gut microbiota composition in Japanese women: a randomised controlled trial. *Eur. J. Nutr.* 58:3291–302

Valentino V, Magliulo R, Farsi D, Cotter PD, O'Sullivan O, et al. 2024. Fermented foods, their microbiome and its potential in boosting human health. *Microb. Biotechnol.* 17:e14428

van den Berg MT, Wester VL, Vreeker A, Koenders MA, Boks MP, et al. 2020. Higher cortisol levels may proceed a manic episode and are related to disease severity in patients with bipolar disorder. *Psychoneuroendocrinology* 119:104658

van Soest APM, Hermes GDA, Berendsen AAM, Van De Rest O, Zoetendal EG, et al. 2020. Associations between pro- and anti-inflammatory gastro-intestinal microbiota, diet, and cognitive functioning in Dutch healthy older adults: the NU-AGE study. *Nutrients* 12:3471

Varun CN, Venkataswamy MM, Ravikumar R, Nagaraju R, Debnath M, et al. 2019. Th17 and MAIT cell mediated inflammation in antipsychotic free schizophrenia patients. *Schizophr. Res.* 212:47–53

Veal C, Tomlinson A, Cipriani A, Bulteau S, Henry C, et al. 2024. Heterogeneity of outcome measures in depression trials and the relevance of the content of outcome measures to patients: a systematic review. *Lancet Psychiatry* 11:285–94

Vijay A, Astbury S, Le Roy C, Spector TD, Valdes AM. 2021. The prebiotic effects of omega-3 fatty acid supplementation: a six-week randomised intervention trial. *Gut Microbes* 13:1863133

Visioli F, Del Rio D, Fogliano V, Marangoni F, Ricci C, Poli A. 2025. Ultra-processed foods and health: Are we correctly interpreting the available evidence? *Eur. J. Clin. Nutr.* 79:177–80

Wang DD, Nguyen LH, Li Y, Yan Y, Ma W, et al. 2021. The gut microbiome modulates the protective association between a Mediterranean diet and cardiometabolic disease risk. *Nat. Med.* 27:333–43

Wastyk HC, Fragiadakis GK, Perelman D, Dahan D, Merrill BD, et al. 2021. Gut-microbiota-targeted diets modulate human immune status. *Cell* 184:4137–53.e14

Watson H, Mitra S, Croden FC, Taylor M, Wood HM, et al. 2018. A randomised trial of the effect of omega-3 polyunsaturated fatty acid supplements on the human intestinal microbiota. *Gut* 67:1974–83

Whelan K, Bancil AS, Lindsay JO, Chassaing B. 2024. Ultra-processed foods and food additives in gut health and disease. *Nat. Rev. Gastroenterol. Hepatol.* 21:406–27

Wiley NC, Cryan JF, Dinan TG, Ross RP, Stanton C. 2021. Production of psychoactive metabolites by gut bacteria. In *Modern Trends in Psychiatry*, ed. CSM Cowan, BE Leonard. S. Karger AG

Yang J, Yuan M, Zhang W. 2024. The major biogenic amine metabolites in mood disorders. *Front. Psychiatry* 15:1460631

Yuan N, Chen Y, Xia Y, Dai J, Liu C. 2019. Inflammation-related biomarkers in major psychiatric disorders: a cross-disorder assessment of reproducibility and specificity in 43 meta-analyses. *Transl. Psychiatry* 9:233

Zhang T, Chen Y, Li X, Zhang J, Duan L. 2024. Genetic associations and potential mediators between psychiatric disorders and irritable bowel syndrome: a Mendelian randomization study with mediation analysis. *Front. Psychiatry* 15:1279266

Zorn JV, Schür RR, Boks MP, Kahn RS, Joëls M, Vinkers CH. 2017. Cortisol stress reactivity across psychiatric disorders: a systematic review and meta-analysis. *Psychoneuroendocrinology* 77:25–36