

Review

The Brain-Gut-Microbiome Axis Across the Life Continuum and the Role of Microbes in Maintaining the Balance of Health

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Abstract

There is a growing body of evidence that the interaction between various microbial organisms and the human host can affect various physical and even mental health conditions. Bidirectional communication occurs between the brain and the gut microbiome, referred to as the brain-gut-microbiome axis. During aging, changes occur to the gut microbiome due to various events and factors such as the mode of delivery at birth, exposure to medications (e.g., antibiotics), environmental exposures, diet, and host genetics. Connections to the brain-gut-microbiome axis through different systems also change during aging, leading to the development of chronic diseases. Disruption of the gut microbiome, known as dysbiosis, can lead to a reduction in beneficial bacteria and a corresponding increase in more harmful or even pathogenic bacteria. This imbalance may predispose or contribute to the development of various health conditions and illnesses. Targeted treatment of the gut microbiome and the brain-gut-microbiome axis may assist in the overall management of these various ailments. The purpose of this review is to describe the changes that occur in the gut microbiome throughout life, and to highlight the risk factors for microbial dysbiosis. We discuss the different health conditions experienced at various stages of life, and how dysbiosis may contribute to the clinical presentation of these diseases. Modulation of the gut microbiome and the brain-gut-microbiome axis may therefore be beneficial in the management of various ailments. This review also explores how various therapeutics may be used to target the gut microbiome. Gut biotics and microbial metabolites such as short chain fatty acids may serve as additional forms of treatment. Overall, the targeting of gut health may be an important strategy in the treatment of different medical conditions, with nutritional modulation of the brain-gut-microbiome axis also representing a novel strategy.

Keywords: gut-brain axis; microbiome; dementia; depression; gut biotics

1. Introduction

1.1 Brain-Gut-Microbiome Axis

A variety of microorganisms are found throughout the human body, including bacteria, viruses, fungi, archaea, and protozoa; together, these comprise the human microbiome [1]. The microbiome refers to the collection of genomes from all microorganisms present in the environment, while the microbiota usually refers to all microorganisms found within a specific environment, including bacteria, viruses, and fungi. The largest population and most diverse community of microbes in humans is found in the gastrointestinal (GI) tract, widely known as the gut microbiome (GM). The GM is considered a virtual organ and can weigh up to 1.5 kg, with the most common species belonging to the phyla Firmicutes and Actinobacteria, and in particular the genera *Bacteroides* and *Bifidobacterium* [2,3]. Throughout life, a variety of factors and exposures can shift the microbial population within the gut, which is often referred to as microbial dysbiosis [4]. Disruptions in the GM can alter the metabolites they produce, such as short-chain fatty acids (SCFAs), and even neurotransmitters that affect the brain through the brain-gut-microbiome (BGM) axis [5,6].

The BGM axis refers to the interaction between the GM and the human host. This occurs through a variety of mechanisms that can impact the brain to influence mood, behavior, and cognitive function (Fig. 1) [7]. The BGM axis involves bidirectional communication, via the vagus nerve, through immune and inflammatory pathways, neurotransmitters, microbial by-products, neuroendocrine signaling, enteroendocrine signaling, and the stress response pathway (hypothalamic-pituitary-adrenal [HPA] axis) [7–11].

1.2 Direct Neural Signalling Through the Vagus Nerve

The vagus nerve interacts with the GM, allowing information to be transferred to and from the central nervous system [12,13]. Several studies have examined the influence of bacterial populations on mood and anxiety. Certain species of bacteria, such as *Lactobacillus rhamnosus* JB-1, were shown to reduce stress-induced anxiety and depression in mouse studies. However, these benefits were reduced in animals that underwent a vagotomy [14]. It has also been reported that individuals treated for peptic ulcer disease with a full truncal vagotomy had a decreased risk of developing Parkinson's disease [15], suggesting a possible role for the vagus nerve in various neurological conditions.



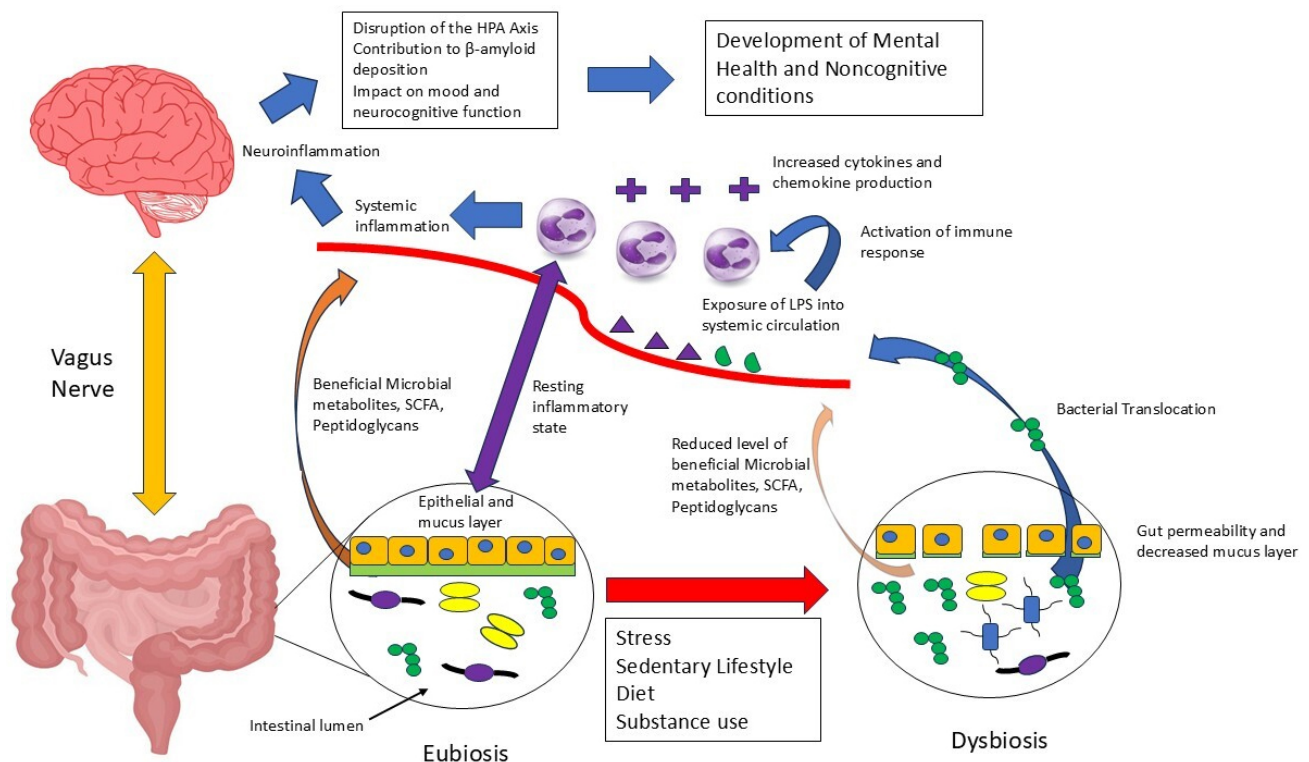


Fig. 1. Microbial dysbiosis and its influence on the brain-gut-microbiome axis. This axis forms a bidirectional communication channel between the brain and the gastrointestinal tract through the vagus nerve. Communication can occur through multiple mechanisms, including the release of microbial metabolites, short-chain fatty acids (SCFAs), peptidoglycans, lipopolysaccharides (LPS), and even neurotransmitters. Endocrine messengers via specialized cells in the epithelial layer (enteroendocrine cells) are also utilized. During eubiosis, there is a resting inflammatory state between the gut microbiome and the host immune system. Disruption of this state (red arrow) can lead to dysbiosis. Factors such as stress can impact the epithelial and mucus layer, resulting in bacterial translocation into the systemic circulation. This can lead to exposure of the immune system to bacterial products, such as LPS, causing activation of the host immune system and systemic inflammation. Subsequently, the resulting neuroinflammation can give rise to mood and cognitive changes, alterations to the hypothalamic-pituitary-adrenal axis, and β -amyloid deposition. These changes may contribute to the development of mental health and neurocognitive conditions. This image was created using Microsoft PowerPoint (Microsoft 365, Microsoft, Redmond, WA, USA). HPA, hypothalamic-pituitary-adrenal.

1.3 Interaction With Immune and Inflammatory Pathways

A resting inflammatory state is needed to maintain and regulate bacteria populations in the GI tract. Under this condition, the GM stimulates immune cells to release various cytokines and chemokines [16], which help prevent the potential spread of bacteria throughout the body. Thus, the immune system contributes to the development of a healthy GM [17]. The development and composition of the GM can change throughout an individual's life from infancy to old age. This process may be essential for the overall function and maturation of the host immune system [18]. At the time of birth, the immune system is relatively immature, and its subsequent exposure to foreign challenges causes it to develop further [19]. With aging, declines in both immune system function and healthy GM populations can predispose elderly patients to oxidative and inflammatory disorders, suggesting that an intricate link exists between the human immune system and the GM [18].

The immune system and GM regulate each other through the epithelial layer of the gut, enterocytes, and Toll-like receptors [20,21]. Various mechanisms exist through which the GM can prevent bacterial overgrowth, pathogen colonization, and damage/infection to the host. Gut bacteria are able to establish colonization resistance whereby the commensal microbiota help to prevent potential invading organisms from competing for resource availability and niche opportunities [17]. This competition is achieved through communication between bacterial cells that sense population density, and subsequently adjust gene expression in a process known as quorum sensing [17,22]. These changes produce chemical signals that result in phenotypic changes in the bacteria, thereby influencing adherence, motility, intestinal density, and the secretion of protective compounds. Quorum sensing has also been associated with gut hemostasis [17]. However, most studies to date have been conducted *in vitro*, which has only lim-

ited ability to fully replicate the complex, dynamic interactions found within the living gut environment. *In vivo* studies are necessary to investigate the multifactorial nature of host-microbe interactions, including immune responses, gut motility, and the diverse microbial community that are difficult to replicate outside the body. Therefore, while *in vitro* models can provide valuable insights, their findings must be interpreted with caution until further *in vivo* studies confirm these mechanisms in the context of the entire gut ecosystem.

The gut epithelial layer is also important in providing protection from invading pathogens and infections. This layer serves as a barrier that separates commensal bacteria in the gut from the host via a monolayer of cells connected through tight-junction protein complexes [17]. The gut epithelial layer, and in particular the tight-junction complexes, can be disrupted by toxins released by certain bacteria [23]. An important component of this barrier is the mucus layer, which acts as a form of reinforcement. Both the mucus and epithelial layers serve as first lines of defense to protect the host from invasion, including translocation of the commensal bacteria into the systemic circulation [24]. However, prolonged periods of stress can increase inflammation and adversely impact the intestinal barrier. This leads to bacterial translocation and an increased level of plasma LPS, thereby activating the immune response [25]. It can also lead to activation of the hypothalamic-pituitary-adrenal (HPA) axis and have an impact on blood brain barrier permeability [10,26], resulting in a chronic neuroinflammatory state. Several studies have reported that neuroinflammation may play a role in various mental health and neurological conditions, including Alzheimer's disease, schizophrenia, obsessive-compulsive disorder, and post-traumatic stress disorder [27–30].

1.4 Neurotransmitters and Microbial By-Products

Bacterial populations in the GM have been found to produce various bioactive compounds, such as bacteriocins, bile acids, choline, and SCFAs [16]. In particular, the production of SCFAs is important for microglial function in the brain. SCFAs are involved in various mental health conditions, such as anxiety, depression, and Alzheimer's disease [31,32]. Various gut bacteria have also been shown to produce several different neurotransmitters, such as gamma-amino butyric acid (GABA) (*Lactobacillus* and *Bifidobacterium*), norepinephrine (*Escherichia*, *Bacillus*, and *Saccharomyces* spp.), dopamine (*Bacillus*), acetylcholine (*Lactobacillus*), and serotonin (*Escherichia*, *Enterococcus*, *Candida*, and *Streptococcus*) [11,33]. Other bacterial populations play a key role in the metabolism of tryptophan, which is a precursor of serotonin [34]. Changes in the levels of bacterial metabolites could serve as possible markers for disease diagnosis and outcome [35].

1.5 Neuroendocrine and Enteroendocrine Signalling

The GM is also involved in various neuroendocrine and enteroendocrine signaling pathways via the BGM axis. The vagus nerve (specifically afferent fibres) communicates with the central nervous system (CNS) via chemosensing through gut endocrine cells [36]. Specific cells known as enteroendocrine cells (EEC) respond to signals from the gut bacteria, causing them to release neuropeptides and hormones such as orexin and ghrelin, which influence peripheral neural communication, and also act centrally to impact behavior [16,36].

2. Changes in the Gut Microbiome Over Time

The intrauterine environment was originally thought to be a sterile environment. However, microbial DNA has been found in the placenta (controversial based on current literature) [37], amniotic fluid [38], umbilical cord [39], and the meconium of neonates born via Cesarean section [40]. A study by Li *et al.* (2020) [41] examined the possibility of a fetal intestinal microbiome. by determining if bacterial DNA and even microbial metabolites could be detected in the second trimester from human intestinal samples. The study was unable to amplify bacterial DNA, however, they were able to establish a fetal metabolomic intestinal profile, with findings suggestive of bacterial and host-derived metabolites that are often produced in response to the microbiota [41]. The authors of this study hypothesize that these microbial-associated metabolites originate from the maternal microbiome and are vertically transmitted to the fetus in order to prime the fetal immune system and prepare the fetal GI tract for microbial encounters postnatally [41]. Moreover, the acquired microbiome may be influenced by the birth route (vaginal delivery versus Cesarean section). Coelho *et al.* (2021) [42] found that infants born via vaginal delivery had a greater abundance of bacteria belonging to the *Bacteroides*, *Bifidobacteria*, and *Lactobacillus* genera whereas those born via Cesarean section were colonized with bacteria similar to those found on the maternal skin and even within the hospital environment, which are primarily the *Staphylococcus*, *Streptococcus*, and *Clostridium* species. A study by Zhou *et al.* (2023) [43] looked at the use of a vaginal microbiota transfer (VMT) for newborns delivered via Cesarean section and found that infant neurodevelopment was significantly higher at 6 months in those that received the VMT compared to a placebo control (saline). Infant neurodevelopment was assessed using the Ages and Stages Questionnaire (ASQ-3) and at 6 months the total score in the VMT group increased by 10.09%; significantly higher than that in the control (Con) group (mean difference (MD) of VMT-Con, 24.87; 95% confidence interval (95% CI): 5.16–44.58; $p = 0.014$) [43]. It has been overall, it has been suggested that the microbiomes of infants born vaginally differ from infants born via cesarean-section and that these disruptions can last from 6 months

Table 1. Factors that influence the gut microbiome at different stages of life.

Stage of development	Factors affecting the gut microbiome
Pediatric (prenatal, neonate, infant, child, adolescent)	• Maternal health status • Maternal diet and microbiome • Intra-uterine environment • Delivery method (vaginal versus Cesarean section) • Gestational age at delivery • Type of feeding (breast or formula) • Exposure to animals • Exposure to other children (siblings, daycare, etc.) • Puberty
Adulthood	• Health status • Diet • Activity level • Sexual activity • Substance use
Elderly/geriatric	• Healthy versus frail • Living situation (independent, community living, supported living, etc.) • Polypharmacy
Throughout life	• Host genetics • Geographical location • Diet • Substance use • Lifestyle (active versus sedentary) • Infections and antibiotic use • Stress (acute versus chronic)

[44] up to 7 years [45] and alterations can be associated with increased risk for disease [43].

The composition of the GM changes with age, particularly during the first few years of life. A study of the GM in 1-year-old children by Odamaki *et al.* (2016) [46] found abundant bacteria from the Actinobacteria phylum, which decreased following weaning and then approached a more adult-like GM profile by the age of 3 years. One study has reported that the GM continues to develop throughout childhood and adolescence [47]. Hollister *et al.* (2015) [47] found that the fecal microbiota of adolescents was similar to that of adults, comprising predominantly Bacteroidetes and Firmicutes. From adolescence onwards, the overall adult GM appears to be more stable, with Firmicutes being the predominant phylum [46]. A variety of factors can influence the overall composition of the GM [35], depending on the stage of development of the individual (Table 1). In the pediatric population, important factors are the infant feeding method (breast versus formula), the presence of pets in the family home, and attendance at daycare. In adolescence and adulthood, the influencing factors can be related to the environment (e.g., air pollution), medication exposure (e.g., antibiotics), and lifestyle (e.g., dental hygiene, alcohol intake, smoking exposure, and physical activity level) [35]. Throughout life, the circadian clock and the GM are important in maintaining metabolic homeostasis. Circadian rhythms help to regulate cell and organ

functions and synchronize physiology with external cues to establish metabolic homeostasis. In particular, a number of these mechanisms occur in the GI tract and are important for nutrient transport, processing, and detoxification [48]. It has been suggested that the circadian clock and gut microbiota influence each other reciprocally, and that gut dysbiosis can lead to circadian asynchrony, thus impacting the homeostasis in either system [48]. Geographical location also appears to have a strong influence on the variation observed in the human gut microbiota [49–51]. However, it should be highlighted that this evidence was mostly obtained from comparisons across different countries and continents with varying levels of urbanization and included populations with different ancestral backgrounds [49]. Indeed, the host genotype may play a role in determining the population and composition of the GM [52]. The most profound modulator of the composition and function of the human GM is likely to be an individual's diet [53]. Dietary intervention has been shown to cause rapid changes in the GM within the first 24 hours. However, these changes tend to be transient, and the distinct bacterial groupings of the core microbial profile are thought to remain stable throughout any intervention [54].

Disruptions to the GM (dysbiosis) can occur throughout an individual's life, with many of these microbiome changes leading to various health conditions (Table 2, Ref. [55–71]). Dysbiosis can influence numerous various physi-

cal and mental health conditions through bidirectional communication with the brain, enteric nervous system, vagus nerve, and microbial metabolites via the BGM axis. These changes can occur throughout life, contributing to chronic inflammation and disease [72]. This review focuses on how dysbiosis can impact a multitude of illnesses afflicting the pediatric population through to the geriatric population. Overall, the GM appears to be an important target in the treatment of disease, opening the way for modulation using probiotics. Methods that promote the return of the GM to a more eubiotic state may help to improve GM-related health conditions.

3. Literature Search

We conducted a literature search using the electronic databases MEDLINE (1966–November, 2024), EMBASE and SCOPUS (1965–November, 2024), and DARE (1966–November, 2024). The main search items were gut bacteria; gut microbiome; gut microbiota; gut dysbiosis; gut probiotics; and pediatric, adult, and geriatric medical conditions.

4. Dysbiosis in the Pediatric Population

Alterations in the GM are often referred to as gut dysbiosis/microbial dysbiosis, leading to an imbalance in microbial populations. This imbalance can also affect the by-products produced by microbes, such as SCFAs and neurotransmitters that influence the brain through the BGM axis. During pregnancy, dramatic changes occur in the maternal microbiota in parallel with brain development in the fetus [73]. An increased abundance of Proteobacteria and Actinobacteria was found in pregnant women, thus promoting energy storage to support fetal growth [65]. In non-pregnant women, this type of microbial dysbiosis would be associated with metabolic syndrome. The GM is believed to play an important role in brain development due to its indirect effect on tryptophan metabolism, which serves as a precursor for serotonin synthesis [74]. The establishment of a healthy GM is therefore vital for fetal development and growth into infancy. Disruption of the GM/dysbiosis has been observed to affect various health outcomes [75].

4.1 Allergies and Asthma

There is emerging evidence that the development of asthma and even allergies are associated with microbial dysbiosis. Early-life exposure to antibiotics has been suggested to be a risk factor for childhood asthma. A study presented at the 2025 American Academy of Allergy Asthma and Immunology/World Allergy Organization (AAAAI/WAO) Joint Congress screened the electronic medical records of 14,807 healthy, full-term children born to mothers with positive Group B Streptococcus vaginal culture between 2006 and 2018. A total of 311 children received antibiotic treatment, which was associated with a significantly higher risk of asthma both in a regression model (relative risk (RR) = 1.3, 95% confidence interval

(CI): 1.04–1.6, $p = 0.018$) and in a propensity model (RR = 1.31, 95% CI: 1.01–1.69, $p = 0.039$) [76]. Children exposed to antibiotics early in life also had higher rates of short-acting beta-agonist (SABA) use and allergic rhinitis. The study concluded that postnatal antibiotic therapy for maternal indication, not confounded by infant infections, was associated with an increased risk of childhood asthma [76]. Penders *et al.* (2007) [55] reported that infants colonized with *Escherichia coli* had a higher risk of developing eczema, while those colonized with *Clostridioides* (previously *Clostridium*) *difficile* were more likely to develop atopic outcomes, including eczema, recurrent wheeze, and allergic sensitization. *C. difficile* was also reported to lead to the development of asthma at around 6 years of age, even when the individual was colonized at 1 month of age [77]. During an infection, the beneficial gut bacteria are replaced by pathogenic *C. difficile* bacteria. The reduction in bacterial diversity may interfere with the development of immunogenic tolerance, resulting in the absence of normal immunosuppressive mechanisms by regulatory T-cells [77]. The subsequent imbalance between T-Helper 1 and T-Helper 2 cells can lead to T-Helper 1- and T-Helper 2-mediated inflammatory diseases, such as allergies and asthma [77]. Antibiotic exposure, particularly during the first year of life, can impact development of the gut microbiota, leading to an increased risk of asthma in children [78].

4.2 Metabolic Conditions

Microbial dysbiosis has been associated with various metabolic conditions, including obesity. This has also been observed in children, and infants with low levels of *Bifidobacterium* spp. and increased *Staphylococcus aureus* were found to be more likely to be overweight by the age of 7 years [56]. Other studies have found that obese children have larger SCFA-producing bacterial populations [79], while children with a normal body-mass index (BMI) have more *Bifidobacterium* spp. in their gut during their first year of life compared with those with a higher BMI [80].

Gut dysbiosis has also been linked to type 1 diabetes mellitus (T1DM). In a study by Yuan *et al.* (2022) [81], gut microbiota from children with T1DM were transferred into antibiotic-treated mice, resulting in elevated fasting glucose and reduced insulin sensitivity in the test animals. The same study also showed that LPS induced a pancreatic inflammatory response, while SCFAs and butyrate induced expression of the *insulin1* and *insulin2* genes [81]. Individuals with type 2 diabetes mellitus (T2DM) and metabolic syndrome (MetS) displayed significant changes in their gut microbiota at both the genus and family levels. In particular, the relative abundance of *Faecalibacterium* and *Oscillospora* was higher in the MetS population, while an increased abundance of *Prevotella* and *Dorea* was seen in the T2DM group compared with controls [57]. This study also

Table 2. Selected studies showing changes in the gut microbiome in various health conditions.

Demographic	Health condition	Change in the gut microbiome	Study
Pediatric	Allergies and asthma	Increased <i>Clostridioides difficile</i>	Penders <i>et al.</i> (2007) [55]
	Obesity	Decreased <i>Bifidobacterium</i> spp. Increased <i>Staphylococcus aureus</i>	Kalliomäki <i>et al.</i> (2008) [56]
	Metabolic syndrome	Increased <i>Faecalibacterium</i> and <i>Oscillospora</i>	Carrizales-Sánchez <i>et al.</i> (2023) [57]
	Type 2 diabetes mellitus	Increased <i>Prevotella</i> and <i>Dorea</i>	Carrizales-Sánchez <i>et al.</i> (2023) [57]
	Autism spectrum disorder	Increased <i>Bacteroidetes</i> Decreased <i>Firmicutes</i>	Finegold <i>et al.</i> (2010) [58]
	Attention deficit hyperactive disorder	Decreased <i>Faecalibacterium</i> and <i>Veillonellaceae</i>	Wan <i>et al.</i> (2020) [59]
Adult	Hypertension	Increased <i>Bacteroides</i>	Yang <i>et al.</i> (2015) [60]
	Crohn's disease	Increased Enterobacteriaceae and <i>Ruminococcus gnavus</i> Decreased <i>Faecalibacterium prausnitzii</i> , <i>Bifidobacterium adolescentis</i> , <i>Dialister invisus</i> , and <i>Clostridium</i>	Hedin <i>et al.</i> (2014) [61]
	Diabetes mellitus	Decreased butyrate-producing bacteria and <i>Firmicutes</i>	McLean <i>et al.</i> (2015) [62]
	Generalized anxiety disorder	Decreased SCFA-producing bacteria and <i>Firmicutes</i> Increased <i>Fusobacteria</i> and <i>Bacteroidetes</i>	Jiang <i>et al.</i> (2018) [63]
	Depression	Increased <i>Actinobacteria</i> , <i>Proteobacteria</i> , and <i>Bacteroidetes</i> Decreased <i>Firmicutes</i>	Dinan and Cryan (2017) [64] Chen <i>et al.</i> (2018) [65]
			Naseribafrouei <i>et al.</i> (2014) [66]
Geriatric	Normal aging	Decreased butyrate-producing bacteria	Ghosh <i>et al.</i> (2022) [67]
	Alzheimer's disease	Decreased <i>Firmicutes</i> and <i>Bifidobacterium</i> Increased <i>Bacteroidetes</i>	Alkasir <i>et al.</i> (2017) [68] Vogt <i>et al.</i> (2017) [69]
	Mild cognitive impairment	Increased <i>Bacteroides</i>	Saji <i>et al.</i> (2019) [70]
	Parkinson's disease	Increased <i>Ruminococcaceae</i> , <i>Bifidobacteriaceae</i> , <i>Christensenellaceae</i> , and <i>Verrucomicrobiaceae</i> Decreased <i>Prevotellaceae</i> , <i>Lachnospiraceae</i> , and <i>Faecalibacterium</i>	Shen <i>et al.</i> (2021) [71]

SCFA, short-chain fatty acid.

identified positive correlations between *Prevotella*, *Dorea*, *Faecalibacterium*, and *Lactobacillus*, with hypertension, abdominal obesity, and high glucose and triglyceride levels [57].

4.3 Neurodevelopmental Disorders

4.3.1 Autism Spectrum Disorder

A growing number of studies have explored the potential association between GM and the development of autism spectrum disorder (ASD). A greater abundance of Bacteroidetes and lesser amounts of Firmicutes were found in children with autism compared with neurotypical controls [58]. Another study found that children with regressive (late-onset) autism had increased numbers of fecal clostridial species and non-spore-forming anaerobes and microaerophilic bacteria compared with control children [82]. A study by Wan *et al.* (2024) [83] used various microbial markers (taxonomy and genome) to help distinguish children with ASD from typically developing peers, with predicted risk scores significantly correlated to symptoms measured with the Social Responsiveness Scale-2. Ongoing studies are currently needed, however, this may serve as a potential validity of the fecal microbiome being an aid in the diagnosing of ASD [83]. Kang *et al.* (2017) [84] reported improvements in social skills and adaptive behavior following fecal transplantation therapy in children with ASD. A follow-up study of these individuals found that they continued to show improvement in both GI and ASD symptoms 2 years after treatment, along with increased bacterial diversity and a relative abundance of *Bifidobacteria* and *Prevotella* [85]. The authors of this study highlight the need for “double-blind, placebo-controlled randomized trials with a larger cohort” which will be beneficial in supporting the use of fecal transplantation in the treatment for ASD. Thus, further studies are needed. However, these and similar studies are limited by the differences between the metabolic and immune systems of mice and humans. It is often this translational medicine/research that allows the results from these animal studies to be applied to human diseases/conditions.

4.3.2 Attention Deficit Hyperactive Disorder

Several studies have investigated the association between the GM and the development of attention deficit hyperactive disorder (ADHD). Disruptions in the GM have been reported in children with ADHD, with a lower abundance of *Faecalibacterium* and Veillonellaceae, and significantly increased levels of *Enterococcus* and *Odoribacter* [59]. *Faecalibacterium* has been associated with anti-inflammatory effects. A decreased abundance of these bacteria may therefore lead to higher levels of inflammatory factors that contribute to ADHD [86]. Another study found that children with ADHD had an increase in *Clostridium*-like species and a decrease in butyrate-producing bacteria compared with healthy children [87].

4.4 Gastrointestinal Disorders

4.4.1 Infantile Colic and Non-Specific Abdominal Pain

Infantile colic is often associated with prolonged periods of crying with no identifiable cause. Some of the proposed causes include GI, psychological, or potentially neurodevelopmental factors [88]. One recent study suggests that gut dysbiosis may contribute to infantile colic, with an increased population of *Proteobacteria* and a reduction in *Lactobacillus* and *Bifidobacterium* [89].

Abdominal pain is a frequent complaint in children. In many cases a specific cause cannot be identified, and it may be associated with conditions such as irritable bowel syndrome (IBS). Rigsbee *et al.* (2012) [90] found that children diagnosed with IBS had a greater abundance of *Prevotella*, *Lactobacillus*, *Veillonella*, and *Parasporo*, and a reduced number of *Verrucomicrobium* and *Bifidobacterium*. Children may also experience episodes of constipation in association with the abdominal pain, with a proportion being functional with no etiology identified. The GM has been investigated as a potential contributing factor, with a cross-sectional pilot study conducted on children with obesity and suffering from constipation. This found a lower abundance of *Prevotella* and an increased number of butyrate-producing bacteria (*Roseburia*, *Coprococcus*, and *Faecalibacterium*) in such individuals compared with controls [91]. The authors speculated that the observed changes in the GM may be related to a diet lower in fiber in these children.

4.4.2 Necrotizing Enterocolitis

Necrotizing enterocolitis (NE) is a condition in which inflammation of the intestine can lead to bacterial translocation, resulting in cellular damage, death, and necrosis of the colon and intestine. It has been suggested that microbial dysbiosis in the preterm neonate may be associated with a higher risk of NE, as well as to complications from this condition [92]. In particular, low microbial diversity may allow the overgrowth of pathogenic bacteria, which is a major risk factor for the development of NE [93]. An increased abundance of *Citrobacter koseri* and/or *Klebsiella pneumonia*, along with reduced diversity in preterm infants, has also been associated with NE [94]. In addition, a lower abundance of *Lactobacillus* and an altered microbial-network structure were observed during the first few days of life [94]. Oral administration of probiotics was found to significantly reduce the incidence of NE [95].

5. Dysbiosis in the Adult Population

A variety of factors can impact the GM and lead to potential dysbiosis during adulthood (Table 1). These may be related to lifestyle factors, such as activity level, stress, medication, and diet. However, even substance use and sexual activity can affect the microbial composition [35]. Cigarette smoking can disrupt both the oral and intestinal GM, but both of these improve following cessation [96,97].

Chronic alcohol consumption can lead to a reduction in *Clostridia*, *Bacilli*, and Bacteroidetes, and an increase in Gammaproteobacteria [98]. It can also impact intestinal mucosal integrity and the BGM axis, leading to mental health conditions such as depression, anxiety, and cravings [98,99].

Adults often experience disruptions in the amount and quality of sleep, and prolonged sleep disturbance can impact the GM [100]. Improvements in sleep efficiency, total sleep time, and good sleep hygiene have been positively correlated with total microbiome diversity, particularly with Bacteroidetes and Firmicutes [100]. With regard to physical activity, individuals with a more sedentary lifestyle were found to have less microbial diversity and more pathogenic bacteria, such as *E. coli*, whereas individuals with a more active lifestyle had more SCFA-producing bacteria [101]. Stress can also impact the GM. Prolonged stress leads to activation of the HPA axis, leading to the release of various hormones and increased inflammation, thereby affecting gut permeability [102]. Dysbiosis can therefore affect a variety of health conditions in adults through alterations of the GM caused by various lifestyle factors.

5.1 Cardiovascular Disease

Several studies have examined the role of the GM in relation to cardiovascular disease [103]. Research has shown the presence of bacterial DNA in atherosclerotic plaques [104], with a possible contribution to the development of cardiovascular disease. GM dysbiosis can reduce the number of butyrate-producing bacteria, thus increasing intestinal permeability and allowing bacterial translocation and increased LPS in the bloodstream [105]. This in turn leads to the activation of various inflammatory pathways that also play a role in the development of atherosclerosis. The oral microbiota observed in periodontal disease has been found to play a role in cardiovascular disease [106,107]. There is current research investigating the association between the GM and heart failure. Bacterial translocation from the gut into the bloodstream can increase the level of endotoxins in the blood, which has been associated with heart failure [108]. Certain bacterial metabolites can also influence heart health. Various cardiac conditions have been associated with altered bacterial populations that generate increased levels of trimethylamine, which can be oxidized in the gut to increase the level of trimethylamine-N-oxide (TMAO) [35].

5.2 Hypertension

The GM has also been linked to hypertension, with a greater abundance of *Bacteroides* found in hypertensive individuals [60]. Hypertension may also affect the GM, leading to dysbiosis. Elevated blood pressure can increase intestinal permeability, with a reduction of SCFA-producing bacteria and increased generation of hydrogen sulfide and

LPS [109]. Overall, the available evidence indicates that dysbiosis is closely related to the occurrence and development of hypertension.

5.3 Gastrointestinal Conditions

Microbial imbalance has often been studied in various GI diseases, in particular inflammatory bowel disease (IBD). A study that examined Crohn's disease amongst siblings found an increased abundance of the Enterobacteriaceae family and *Ruminococcus gnavus*, and a decreased abundance of *Faecalibacterium prausnitzii*, *Bifidobacterium adolescentis*, *Dialister invisus*, and *Clostridium* cluster XIVa [61]. Individuals with Crohn's disease, ulcerative colitis, and ischemic colitis have reduced *Faecalibacterium prausnitzii* and *Prevotella* sp. populations, and increased *Enterococcus faecium*, *Enterococcus faecalis*, and *Escherichia coli* [110]. Individuals with Crohn's disease have altered gut microbiota, along with increased mucin breakdown and epithelial permeability [111]. Breakdown of the mucosal membrane and increased permeability are likely to disrupt one of the first lines of defense of the human host and allow the escape of luminal bacteria, suggesting that this may be a prelude to the development of Crohn's disease [103,111]. Specific bacterial populations are thought to play a key role in the pathogenesis of Crohn's disease, with a reduced number of butyrate-producing bacteria often being observed. The resulting decrease in butyrate level, which is an energy source for epithelial cells, may contribute to degradation of the intestinal epithelial layer [61]. An increased abundance of sulfate-reducing bacteria has also been found in patients with IBD. These metabolize sulfate into hydrogen sulfate, which can affect butyrate consumption and phagocytosis by immune cells, and also kill bacteria, leading to further dysbiosis [112].

5.4 Obesity and Metabolic Conditions

Considerable research has explored the role of the GM in the development and progression of obesity in humans. A specific pattern of microbiota has been observed in obese individuals, typically accompanied by reduced diversity. A reduction in Bacteroidetes and an increase in Firmicutes has been associated with changes in weight and fat distribution, with obese individuals having an abnormally higher ratio of these bacteria [113]. Restoration of the microbial balance, particularly an increase in Bacteroidetes, has been correlated with weight loss in obese individuals. Although the Firmicutes/Bacteroidetes ratio is often cited as a hallmark of obesity, contradictory results have been reported in the literature [114]. These discrepancies may be the result of interpretative bias arising from methodological differences in sample processing and DNA sequence analysis, the generally poor characterization of recruited subjects, and especially the lack of consideration of lifestyle-associated factors known to affect microbiota composition and/or diversity [114]. While some studies have found that gut microbiota may contribute to the development of obesity, the ev-

idence suggesting an association between obesity and alteration of the Firmicutes/Bacteroidetes ratio is not convincing [114].

Changes in the gut microbial populations can also be observed in subjects with diabetes mellitus (DM). Reductions in microbial diversity, butyrate-producing bacteria, and Firmicutes have been observed in both insulin-dependent and non-insulin dependent diabetes, together with increased intestinal permeability in both mice [115] and human studies [116]. Adults with insulin-dependent DM were found to have more abundant Bacteroidetes and *Clostridium*, and reduced *Bifidobacteria*, *Lactobacillus*, and *Prevotella*. Non-insulin dependent DM adults without obesity displayed lower levels of *Clostridium* and Bacteroidetes, and increased *Lactobacillus* [62].

5.5 Cancer

A growing body of evidence suggests that infections, particularly viruses, may play a role in about 20% of all cancers. As one of the most common infectious agents, bacteria are considered an emerging factor for the development of malignant cells [117]. The GM may contribute to the development of certain cancers, such as colorectal cancer (CRC), through various mechanisms including immune modulation and activation of cell proliferation pathways [118–120]. Microbial infections can affect the transformation of host cells and promote the development of malignant features. This can occur through the production of carcinogenic metabolites that participate in the inflammation response, leading to disruption of cell metabolism and genomic or epigenetic changes [117]. Dysbiosis can reduce protective bacteria and increase the abundance of pathogenic and cancer-promoting bacteria (*Streptococcus bovis*, *Sulfidogenic* bacteria, *Fusobacterium nucleatum*, *Bacteroides fragilis*, *Clostridium septicum*, *Escherichia coli*, *Helicobacter pylori*, *Enterococcus faecalis*) and viruses (human papilloma virus, John Cunningham virus, and Epstein Barr virus) [35,120]. Adults with CRC show a decrease in butyrate-producing bacteria, with increased levels of Firmicutes, Bacteroidetes, Enterobacteriaceae, and Fusobacteria [121]. Two bacterial species, *Akkermansia muciniphila* and *Fusobacterium nucleatum*, are often increased in CRC biopsy samples. *Fusobacterium* may be an opportunistic pathogen at immune-compromised sites. Recent studies have examined the use of *F. nucleatum* as a biomarker in the detection for GI malignancies. A Meta-analysis by Huangfu *et al.* (2021) [122] determined that elevated levels of *F. nucleatum* in tumor tissue were strongly associated with lower overall survival, disease-free survival, and cancer-specific survival in CRC patients. Thus, the detection and determination of the overall abundance of *F. nucleatum* in various patient samples (stool, saliva) may aid in the detection and diagnosis of certain GI malignancies and potential help prognosis monitoring (Yu *et al.* 2024) [123].

5.6 Multiple Sclerosis

There is evidence that disruption in the GM may play a role in certain inflammatory-mediated diseases. Multiple sclerosis (MS) is a chronic inflammatory neurodegenerative condition with a strong autoimmune component. A systematic review by Ordoñez-Rodríguez *et al.* (2023) [124] found that adults with MS had an altered GM compared with controls. This included decreases in the abundance of Firmicutes, *Lachnospiraceae*, *Bifidobacterium*, *Roseburia*, *Coprococcus*, *Butyricicoccus*, *Lachnospira*, *Dorea*, *Faecalibacterium*, and *Prevotella*; increases in Bacteroidetes, *Akkermansia*, *Blautia*, and *Ruminococcus*; and a reduction in the amount of SCFAs, particularly butyrate producing bacteria [124]. It was hypothesized that such alterations in the GM may lead to the chronic inflammation seen in MS.

5.7 Mental Health Conditions

There is growing evidence for involvement of the GM and BGM axis in various mental health conditions, such as anxiety, depression, bipolar disorder, and schizophrenia [6]. Putative associations between the microbiota and psychiatric disorders are multifaceted and involve complex mechanisms, including the regulation of neurotransmitters, modulation of the immune system, influence on the stress response, and production of microbial metabolites that affect brain function. Neuroimaging is not commonly used in studies examining the effects of probiotics on mental health due to the complex and indirect interaction of the BGM axis. Probiotics primarily affect the gut by influencing microbiota composition, immune function, and gut barrier integrity. These changes do not always result in measurable brain activity detectable by neuroimaging, although some studies have used neuroimaging to evaluate the effects of probiotics. A systematic review by Crocetta *et al.* (2024) [125] of task-based functional magnetic resonance imaging (fMRI) studies in healthy individuals revealed that probiotics can modulate brain activity related to emotional regulation and cognitive processing. Moreover, task-based fMRI studies in clinical populations showed that probiotics could normalize brain function in patients with major depressive disorder and IBS [125].

5.7.1 Depression, Anxiety, and Obsessive-Compulsive Disorder

Compared with healthy controls, adults with major depressive disorder were found to have increased populations of Actinobacteria, Proteobacteria, and Bacteroidetes, but decreased levels of Firmicutes [64–66]. Changes in the GM may also play a role in depression through the BGM axis, and hence strategies that normalize the microbial balance using probiotics may help with treatment [126,127]. Individuals with generalized anxiety disorder were found to have decreased levels of SCFA-producing bacteria, decreased Firmicutes, and increased *Fusobacteria* and Bacteroidetes [63]. Alterations in microbial populations can

affect the concentrations of various metabolites, such as phenylalanine, tyrosine, and tryptophan, which are important components of serotonin metabolism and BGM axis signaling [128,129]. Studies on patients with obsessive-compulsive disorder (OCD) have found that microbial dysbiosis influences the BGM axis through changes to neurotransmitters [30,130]. There is also emerging evidence that neuroinflammation may play a role in conditions such as OCD, which may be the result of bacterial translocation causing the activation of systemic immune and inflammatory processes [30].

5.7.2 Bipolar Disorder and Schizophrenia

In addition to depression and anxiety disorders, the BGM axis and microbial dysbiosis may be involved in bipolar disorder and schizophrenia. The GM could play a role in the chronic inflammation that is often seen in patients with bipolar disorder [131]. These patients showed decreased *Faecalibacterium* populations and increased *Flavonifractor* compared with healthy controls [132,133]. Both treated and nontreated schizophrenia patients show altered gut microbiota, with the abundance of certain bacterial phyla such as Veillonellaceae and Lachnospiraceae being related to disease severity [134]. Another study showed that patients presenting with a first episode of psychosis had altered levels of *Lactobacillaceae* compared with the healthy controls [135].

5.7.3 Personality Traits

There is some recent evidence to suggest that the GM and BGM axis may affect personality. Kim *et al.* (2018) [136] found that microbiota diversity is related with certain personality traits. Individuals with greater neuroticism or low conscientiousness showed a high abundance of Gammaproteobacteria and Proteobacteria, respectively [136]. Individuals that exhibited more conscientiousness were also found to have an increased abundance of some universal butyrate-producing bacteria, including Lachnospiraceae [136].

6. Dysbiosis in the Geriatric (Older Adult) Population

As with pediatric (younger) and adult populations, multiple factors can affect the GM in elderly patients, leading to dysbiosis and alterations to the BGM axis (Table 1). While many of these factors can occur together, it should be noted that polypharmacy, poorer living conditions, frail health, and aging itself can contribute to dysbiosis. Medication with antibiotics have the greatest impact on the GM, although drugs such as proton pump inhibitors, antidepressants, antipsychotics, Non-steroidal Anti-inflammatory Drugs (NSAIDs), and opioids can also cause dysbiosis [35]. Some medications, such as metformin and statins, may have a positive impact on the GM. Metformin promotes SCFA-producing bacterial growth [137], while improvement of the GM by statins may enhance the therapeutic effects of

these medications [138]. In brief, changes to the human GM can affect the development and/or progression of certain physical and neuropsychiatric conditions.

6.1 Healthy Aging

A variety of changes occur in the GI tract during the normal aging process, including decreased colonic motility, decreased absorption of certain vitamins, and bacterial overgrowth. Healthy older individuals show a reduction in the more prominent butyrate-producing bacteria, such as *Faecalibacterium*, *Roseburia*, *Coprococcus*, and *Eubacterium* spp. (especially *E. rectale*) [67]. Butyrate may have important roles during healthy aging, such as preventing inflammation, improving intestinal barrier function, serving as an energy source for colonocytes, and suppressing endocannabinoid-regulated adipogenesis, insulin resistance, cognitive decline, and cancer onset [67].

6.2 Neurocognitive Disorders

Studies of older adults with neurocognitive disorders such as Alzheimer's disease (AD) have found a decreased abundance of Firmicutes and *Bifidobacterium*, along with increased Bacteroidetes. Such changes may increase the risk of dementia [68,69]. A higher abundance of *Bacteroidetes* was also found in patients with mild cognitive impairment (MCI) [70]. Gut dysbiosis has been hypothesized to play a role in amyloid pathogenesis, which forms part of the disease process observed in AD. LPS and *E. coli* have been found in amyloid plaques from brain tissue samples of patients with AD [139]. The BGM axis could therefore be involved in the development of AD. Increased gut permeability allows bacterial LPS translocation, thus stimulating the systemic immune system and leading to neuroinflammation [69]. A chronic neuroinflammatory state may lead to deposition of β -amyloid in the brain. Moreover, microbial dysbiosis can reduce the bacterial population that produces SCFAs. These are important for microglial phagocytic function, resulting in defective amyloid clearance [140,141].

Cognitive decline is often associated with behavioral and psychological symptoms of dementia (BPSD), such as perceptual disturbances, as well as affective and impulse control behaviors. Disruptions in eating are common, which can then influence the GM and the BGM axis and potentially contribute to BPSD [142,143].

6.3 Parkinson's Disease

Parkinson's disease (PD) is the second most common neurodegenerative disease affecting older adults. It is often characterized by motor dysfunction due to the degeneration of dopamine-producing neurons in the brain, primarily in the substantia nigra. Evidence from animal studies suggests that the BGM axis may be involved in the onset and progression of PD through an increase in intestinal permeability, aggravation of neuroinflammation, abnormal α -synuclein

fibrils, increased oxidative stress, and a decrease in neurotransmitter production, particularly dopamine [144,145]. Disruption of the bacterial populations in PD patients have been reported, with a higher α -diversity [146]. Significant decreases were observed in Prevotellaceae, Lachnospiraceae, and *Faecalibacterium* in PD patients compared with individuals without PD, whereas Ruminococcaceae, Bifidobacteriaceae, Christensenellaceae, and Verucomicrobiaceae were increased [71]. A meta-analysis reported that PD patients show an increased abundance of *Megasphaera* and *Akkermansia*, and a reduced abundance of *Roseburia* [147]. Among the studies that examined the GM in PD patients, the most consistently reported change was a reduction in Prevotellaceae [145]. It was speculated that decreased levels of Prevotellaceae can lead to the development of α -synucleinopathies due to reduced production of SCFAs. Lower levels of SCFAs have been found in patients with PD compared with healthy controls [148]. The decreased SCFA concentration can affect intracellular and extracellular protein clearance mechanisms associated with SCFA-dependent gene expression [149]. Furthermore, reductions in SCFAs such as butyrate can affect the expression of occludin, a key tight junction protein. This leads to intestinal permeability and endotoxin exposure, resulting in overexpression and aggregation of α -synuclein, which is a major component of PD pathogenesis [145]. In addition to butyrate, other SCFAs such as acetate and propionate are also involved in BGM axis communication and can modulate α -synuclein aggregation [148]. These findings highlight how the BGM axis may be an important component in the development and progression of PD.

6.4 Stroke

Several studies have indicated that microbial dysbiosis following an ischemic stroke may affect patient outcome. Sun *et al.* (2022) [150] investigated the GM in patients following a stroke. Patients that had a bad outcome showed a reduced α -diversity, with an increased abundance of more pathogenic bacteria such as Enterococcaceae and *Enterococcus*, along with a decrease in SCFA-producing bacteria such as Bacteroidaceae, Ruminococcaceae, and *Faecalibacterium* [150]. In clinical trials that examined the GM in stroke patients, alterations were found in microbial populations, particularly in the Firmicutes-to-Bacteroidetes ratio. An increased abundance of *Megasphaera*, *Enterobacter*, and *Desulfovibrio* was observed, together with a decreased abundance of *Blautia*, *Roseburia*, *Anaerostipes*, *Bacteroides*, *Lachnospiraceae*, and *Faecalibacterium* (SCFA-producing bacteria) [151]. Another clinical study that investigated the GM of patients after cerebral stroke showed a reduced abundance of *Roseburia*, *Bacteroides*, and *Faecalibacterium prausnitzii*, and an increased abundance of Enterobacteriaceae, Bifidobacteriaceae, and *Clostridium difficile* compared with healthy subjects, intensive care patients, and patients with active ulcer-

ative colitis or IBS [152]. A decrease in commensal bacteria and an increase in opportunistic pathogenic bacteria can contribute to a pro-inflammatory state and lead to increased levels of TMAO with reduced SCFAs, thereby contributing to inflammation and atherosclerosis, and increasing the risk of stroke [153,154].

7. Management of Microbial Dysbiosis

Throughout life, the GM encounters a myriad of insults and influences that can disrupt bacterial populations, which in turn disturbs the BGM axis. This imbalance can affect the development and progression of various physical and mental health conditions. Bringing the GM to a more eubiotic state may therefore be a potential therapeutic option. For many of these illnesses, conventional therapy does not always lead to a complete resolution of symptoms, or fully address patient management. Methods that tackle dysbiosis and the BGM axis could thus be considered as potential adjuvant therapy, including dietary modification, gut biotics, or even fecal microbiome transplantation (FMT).

7.1 Diet

Modification of an individual's diet has one of the largest impacts on bacterial populations in the human gut. Certain food products and specific diets have been studied with the aim of restoring bacterial imbalance and managing dysbiosis.

7.1.1 Dietary Modification in Pediatric Populations

Fermented foods have been shown to improve the GM and provide a wide variety of benefits to human health. In a study of 73,522 pregnant Japanese women, Tanaka *et al.* (2024) [155] correlated the consumption of fermented foods (miso soup, fermented soybeans, yogurt, and cheese) with the neurodevelopment of their child during the first year of life. Maternal intake of miso soup and fermented soybeans was associated with a reduced risk of the infant having delays in communication skills, while the intake of fermented soybeans and cheese was associated with a reduced risk of delays in developing fine motor skills, and the intake of yogurt was associated with a reduced risk of delays in developing personal-social skills [155]. A systematic review and meta-analysis examined the role of fermented foods in the treatment of diarrheal diseases in children younger than 5 years. Based on seven randomized-controlled trials (RCTs), the consumption of fermented foods was found to significantly reduce the mean duration of diarrhea by -0.61 days (95% CI, -1.04 , -0.18) and the length of hospitalization by -0.35 days (95% CI, -0.69 , -0.02) compared with non-treated controls, but not the mean daily frequency of bowel movements (-2.00 ; 95% CI, -7.03 , 3.04) [156]. Another study used a porcine model to compare formula-fed versus sow-fed piglets and the impacts on gut health and the GM. Sow-fed groups showed five-fold higher levels of *Lactobacillaceae* spp. and three-fold higher levels of *Clostridia*

spp. compared with formula-fed piglets, while the latter had 5-fold higher levels of Enterobacteriaceae spp. [157]. Formula-fed piglets also showed alterations in GI morphology, microbial abundance, and expression of the intestinal barrier protein VE-cadherin and the anti-inflammatory molecule IL-10 [157]. A human study compared fermented formula with cow milk-based formula (control) and exclusively breast-fed infants [158]. The study examined whether these diets affect the concentration of secretory immune-globulin A (SIgA), which contributes to the development of intestinal immunity. The level of SIgA was found to be significantly higher in the fermented formula-fed infants ($p = 0.03$), with similar amounts to the breast-fed infants [158]. A notable increase in *Bifidobacterium* was observed over time in all three groups, with the microbiota composition and metabolic activity of the gut in the fermented formula-fed group being more similar to the exclusively breastfed group [158]. Current research aims to develop guidelines concerning the use and exposure to fermented foods in the diets of children [159]. Supplementation with some fermented foods, such as fruit kefir, fermented sweet potatoes, apple sauce, and sauerkraut may help to broaden palates and perhaps even reduce the desire for “sweets” [159]. There is also some evidence that consumption of fermented foods, mushroom biomass supplements, and probiotics may help with upset stomach and digestive problems (leaky gut) in children with neurobehavioral disorders such as ADHD, Asperger’s, and processing disorder. This could even help to improve brain function, psychosocial behavior, cognition, and learning ability in such cases [159].

7.1.2 Dietary Changes in Adults and Older Adults

The consumption of fermented food in the adult and elderly population has been found to promote the displacement of pathogenic bacteria within the GM, leading to alterations in the digestibility and tolerance of certain foods, as well as benefits from metabolites related to immune function [160]. Another study suggested that eating more plant-based, fiber-rich food can reduce opportunistic and inflammatory bacteria, and induce a shift to more beneficial bacteria and metabolites [161]. Certain plant-based foods, such as beetroot juice, can affect the GM by increasing the population of *Akkermansia muciniphila* and decreasing *Bacteroides fragilis*, which is thought to have a positive impact on reducing the risk of diabetes and obesity in human subjects [162]. The consumption of orange juice has also shown positive impacts on the GM by promoting more probiotic strains, such as *Bacteroides xylanisolvens*, and reducing the number of *Clostridia* spp. strains [163]. Certain whole fruits, such as kiwis, can influence the GM and improve GI function, including relieving constipation [164]. A more vegan diet that is rich in fiber can help to promote the growth of SCFA-producing bacteria, which in turn inhibits the growth of more pathogenic bacteria [165].

Individuals may consume various types of diets, each of which can affect the GM. Typically, the Western diet is often compared with the Mediterranean diet in relation to health benefits. The Western diet consists of processed food with a higher abundance of salt, saturated/trans fats and sugars, and less fiber-rich foods, whole grains, and fish. This can have a negative impact on the GM, often promoting the growth of endotoxin-producing bacteria [166]. The Western diet can also affect the intestinal epithelial barrier to increase permeability, allowing harmful bacterial components such as LPS to enter the bloodstream and leading to systemic inflammation, which contributes to various health conditions [166].

In comparison, the Mediterranean diet has often been associated with health benefits, including a positive effect on the GM. This diet contains reduced amounts of processed foods and more fruit, vegetables, fish, nuts, and seeds. Meat is also a component, but often at a reduced frequency. The Mediterranean diet also includes more fiber, omega-3 fatty acids, and low-glycemic index foods, and has been associated with reduced risks of cardiovascular disease, diabetes, obesity, cancer, and inflammatory complications [167,168], as well as improvement of the GM. The Mediterranean diet promotes microbial diversity, particularly an increased abundance of *Bacteroides*, *Prevotella*, *Lactobacillus*, *Faecalibacterium*, *Clostridium*, and *Oscillospira*, while decreasing Firmicutes [169]. Dietary modifications and adjustments in the intake of specific foods can therefore help to restore a healthy balance in the GM and improve overall gut health. More direct bacterial modification can also be considered, such as the use of gut biotics.

7.1.3 Gut Biotics: Nutritional Modulation of the Gut Brain Axis

Nutritional modulation of the BGM axis and the gut-organ axis can be achieved using gut biotics [170]. This term is used to describe food or food constituents that affect the GM, or the direct administration of live microbes for the purpose of therapeutic benefit, including probiotics, prebiotics, and synbiotics [171]. Probiotics are live microorganisms, typically bacteria, that help to maintain or restore the gut microbiota. In comparison, prebiotics are non-digestible fibers that help to promote the growth of beneficial gut microbes, while synbiotics are compounds that contain both prebiotics and probiotics to help improve gut health. Postbiotics are metabolic by-products of the gut microbiota, and in particular the crude extracts from these microbes that can elicit a biological response [171]. The term “gut biotics” was coined in the literature by Alagiakrishnan and Halverson in 2021 [171] and refers to food constituents that can affect gut microbes, or to live microbial administration or their products for therapeutic purposes. The term “psychobiotics” has often been used to describe probiotics and prebiotics that can benefit mental health. However, other literature also refers to psychotropics and antibiotics

as part of the psychobiotic class [171]. Currently there is no consensus regarding the definition of psychobiotics, and therefore gut biotics is a more encompassing term when referring to a product that directly influences the GM to promote beneficial effects within the GI tract and throughout the host [171]. Probiotics ferment prebiotic dietary fiber and help to colonize gut probiotic bacteria. They also generate fermented by-products called proteobiotics that affect the growth of enteropathogens by producing inhibitory bacteriocins and lowering the pH. Following completion of their life cycle, the dead remnants of probiotics, such as cell wall glycoproteins, are known as postbiotics. These inhibit the adhesion and biofilm formation of pathogens on the gut epithelium. In addition to the beneficial effects seen in the gut, systemic responses are also observed at different gut-organ axes [172,173].

7.1.4 Probiotics

Probiotics are a commonly used gut biotic consisting of a non-pathogenic microorganism, typically bacterial, that is designed to improve human health. The most commonly used probiotic bacteria belong to the *Lactobacillus* and *Bifidobacterium* genera [174]. Probiotics are used in various individuals and age groups to help treat and manage a number of different health conditions.

Yang *et al.* (2020) [175] examined the role of oral probiotics in pregnant women and in particular their impact on the vaginal microbiota, as vaginal dysbiosis is associated with spontaneous preterm birth. They found a flux in the vaginal microbiome, regardless of the treatment arm (probiotic versus placebo), with no adverse effects noted in the women receiving probiotic treatment. The use of probiotics in pregnancy has been suggested to help reduce the risk of developing gestational diabetes, metabolic syndrome, and preeclampsia [176]. Probiotics in the pediatric population have often been used for the treatment of infectious gastroenteritis, the prevention of antibiotic-associated diarrhea, and for *Clostridioides difficile*-associated and nosocomial diarrhea [177]. In children and adolescents considered to be overweight or obese, treatment with a probiotic was found to improve BMI, adiposity, metabolic parameters, inflammatory markers, fatty liver, transaminase levels, and glucose metabolism [178]. The Probiotics in Pediatric Asthma Management (PROPAM) study reported two strains of probiotics, *Ligilactobacillus Salivarius* LS01 (DSM 22775) and *Bifidobacterium Breve* B632 (DSM 24706), that significantly improved asthma exacerbations and wheezing episodes in children [179].

Multiple studies have examined the role of probiotics in relation to weight gain and obesity in adults. A systematic review by Torres *et al.* (2024) [180] found evidence that probiotic treatment, typically with a combination of strains from the *Bifidobacterium* and *Lactobacillus* genera, can help to reduce excess weight or obesity. Other studies have found that probiotic treatment can al-

leviate functional GI symptoms [181], as well as improve various cognitive and psychiatric symptoms [171]. Den *et al.* (2020) [182] performed a meta-analysis involving 297 subjects with cognitive decline (either MCI or AD) and found a significant improvement in cognition (Standard mean difference (SMD): 0.37; 95% CI: 0.14–0.61; $p = 0.02$) in subjects receiving a probiotic compared with the control group. Patients with a history of major depressive disorder showed improvement in mood symptoms after receiving a probiotic mixture of *Bifidobacterium longum* and *Lactobacillus helveticus* [183]. Moreover, healthy individuals who received this probiotic mixture showed a reduction in obsessive-compulsive sub-scores based on the Hopkins symptom checklist [184]. Hence, despite the limitations, there is some evidence of benefit from probiotics in the treatment of various health conditions. However, not all studies have consistently used the same probiotic strain, which could account for some variation in results. Often there is also strain-specific variability, even amongst members of the same genus. For example, *Lactobacillus rhamnosus* GG (LGG) and *Lactobacillus casei* are both effective probiotics but have distinct strain-specific benefits. LGG is especially well known for its strong immune-modulating effects, ability to prevent diarrhea, and potential benefits in managing stress and mental health, including anxiety and depression. On the other hand, *L. casei* is beneficial for digestive health, improving gut motility, reducing inflammation in GI disorders such as IBS and IBD, and enhancing overall immune function. While both strains support gut health and immunity, their unique mechanisms make them suited for different therapeutic applications. The mode of probiotic delivery (e.g., capsule, tablet, powder, or fermented food) can influence survival of the probiotic culture in the large intestine. Certain probiotic strains may not colonize the gut permanently and must therefore be taken regularly for sustained benefit. Finally, the overall safety of probiotics needs to be considered, due to instances of opportunistic infections occurring in immunocompromised or critically ill individuals [171].

In summary, probiotics are useful in a number of medical conditions affecting adults and pediatric subjects, including genitourinary, skin, mental health, and gut-related conditions. Probiotics are available as fermented foods and commercial probiotic strains. In contrast to commercial products, fermented foods are not strain specific. Probiotics generally lack adverse effects, except on rare occasions when infections may occur in immunosuppressed individuals, and when antibiotic-resistance genes are transferred to other organisms in the gut [185].

7.1.4.1 Role of Probiotics in Healing of the Intestinal Mucosa.

Dysbiosis is involved in the development of chronic inflammation in the intestine, leading to disruption of the mucosal layer and increased gut permeability [186], which is involved in the pathogenesis of a number of medical

conditions. Gut biotics (probiotics, prebiotics, synbiotics, and postbiotics) can help to restore leaky intestinal barrier function. Since dysbiosis contributes to increased gut permeability, interventions that alter the gut microbiota and correct dysbiosis may also restore intestinal barrier function [187] and play a role in intestinal mucosal wound closure [186,188]. Administration of certain strains of probiotics in animals is associated with a reduction in inflammation markers [189]. Recombinant probiotics have also been shown to promote wound healing in the intestinal lumen [190]. Many *in vitro* and *in vivo* studies have demonstrated the positive role of probiotics in mucosal gut homeostasis and intestinal wound healing [187,188,191,192].

7.1.4.2 Role of Probiotics as Bio-Preservatives. Probiotic microorganisms can be used as protective cultures in food preservation and to extend the shelf-life of food. Bio-preservation can occur through the production of metabolic products or post biotics, such as bacteriocins. These foods are broadly classified as functional foods due to their higher functionality in maintaining good human health [193–195].

7.1.4.3 Next Generation Probiotics. Advances in engineering and synthetic biology, such as sequencing, bioinformatics, and omics, have enabled the development of next generation probiotics that can be used to prevent various medical disorders [196].

Whelan *et al.* (2024) [197] reported that only a small number of probiotic and prebiotic trials have provided dietary data. Experts from the International Scientific Association for Probiotics and Prebiotics recommend that dietary factors need to be considered in future probiotic and prebiotic research [197]. In particular, diets that include functional foods are a promising area of research that should be explored in future clinical trials.

7.2 Prebiotics and Synbiotics

Another strategy for restoration of the GM and the BGM axis is to provide a fuel source that promotes the growth of beneficial bacteria in the GI tract. In this regard, prebiotics are designed to provide a direct benefit to the microorganisms, thus improving human health. Certain supplements contain a combination of probiotic and prebiotic agents, known as synbiotics. Typically, dietary fiber is often used as a prebiotic to promote the growth of SCFA-producing bacteria [198]. A systematic review and meta-analysis have evaluated the development of allergies in pregnant women, breastfeeding mothers, and infants following exposure to prebiotics [199]. Although it did not find any studies of prebiotics given to pregnant women or breastfeeding mothers, the use of prebiotic supplementation in infants was found to reduce the risks of developing eczema (RR: 0.68, 95% CI: 0.40 to 1.15), wheezing/asthma (RR, 0.37; 95% CI: 0.17 to 0.80), and food allergy (RR: 0.28, 95% CI: 0.08 to 1.00) compared with con-

trols [199]. Daily administration of oligofructose-enriched inulin for 16 weeks (8 g/day) in a pediatric population was found to reduce weight gain and improve truncal fat disposition and body weight z-scores compared with the placebo group [200]. The use of prebiotics in adults has been found to alter the gut microbial profile, improve gut microbial metabolism and function, and improve host physiology to alleviate diabetes and obesity [201]. It has been suggested that most prebiotics for the gut require a daily oral dose of at least 3 g for any benefit to be appreciated [202]. For fructo-oligosaccharide (FOS) and galacto-oligosaccharide, the daily dietary target has been suggested to be around 5 g [202]. The dose-effect relationship is variable, and while some doses may be beneficial, the optimal amount for achieving metabolic improvement is still under investigation, with potential differences in individual needs.

There is some evidence that the use of gut biotics (both prebiotic and probiotic) in the pediatric population may improve anxiety, stress, and cognition. However, the results of such interventions have been inconsistent between studies [203]. A study involving 40 adult patients with moderate depression were given 20 mg/day of fluoxetine for 4 weeks, then given a synbiotic (plus fluoxetine) or placebo (plus fluoxetine) for 6 weeks. The treatment with the synbiotic was found to have a greater reduction in participant's Hamilton Rating Scale for depression scores (Mean $\pm$ Standard deviation (SD) = -19.25 ± 1.71) compared to the placebo group (Mean $\pm$ SD = -17.75 ± 2.05 ; $p = 0.024$). [204]. However, several limitations were noted with this study, including a short follow-up period, a potentially insufficient sample size, and limited generalizability due to participant demographics. Additionally, the study did not fully address potential confounding variables and further independent research is needed to confirm the findings and strengthen the evidence for synbiotics as an adjunct in the treatment of depression. The use of oligofructose-enriched inulin (a prebiotic) has also been reported to improve cognition, with better performance in recognition memory and both immediate and delayed recall [205]. The use of prebiotics and synbiotics may promote the growth of beneficial bacteria and thus help to restore normal BGM axis function, which could in turn improve many neuropsychiatric symptoms.

7.3 Fecal Microbiota Transplantation

Fecal microbiota transplantation (FMT) is a treatment that transfers fecal bacteria from an otherwise healthy donor to a recipient, with the purpose of repopulating the recipient's GI tract with beneficial bacteria. It is used most notably in the treatment of recurrent *Clostridioides difficile* infections and antibiotic-associated diarrhea (AAD). The use of FMT has also been studied in regard to treatment for obesity and glycemic control. Hu *et al.* (2023) [206] found that individuals treated with FMT showed significantly lower weight (Weighted mean difference (WMD) equals -4.77 , 95% CI: -7.40 – -2.14), BMI (WMD equals -1.59 , 95% CI:

−2.21~−0.97), Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) score (WMD equals −0.79, 95% CI: −1.57~−0.00), and HbA1c (WMD equals −0.65, 95% CI: −0.75~−0.55) compared with their pretreatment data. In animal studies, mice that received FMT from patients with a psychiatric diagnosis, such as anxiety or depression, showed anxiety and depressive-like symptoms, along with behavioral changes [207]. Moreover, patients that received FMT from a healthy donor exhibited less depressive and anxiety-like symptoms [208]. A case report of an 82-year-old patient that received FMT for treatment of infection with *C. difficile* showed improved cognitive function at 6 months post treatment, particularly in memory and the mini-mental status exam (MMSE) [209]. The use of FMT may therefore help to restore microbial balance and serve as a treatment for physical conditions such as obesity and diabetes, as well as mental health disorders including anxiety and depression.

7.4 Microbial Metabolites: Short-Chain Fatty Acids (SCFAs)

Bacteria within the gut are involved in various biochemical processes and produce different metabolites, of which SCFAs are an important component of the BGM axis. SCFAs are generated by bacteria in the microbiota through the anaerobic fermentation of dietary fibers. Acetate, propionate, and butyrate represent more than 95% of the colonic SCFAs, where they are found at a molar ratio of approximately 60:25:15 under healthy conditions [210,211]. SCFAs mediate local protective effects in the gut through regulation of intestinal mucosal immunity, intestinal motility, and gut barrier integrity, as well as mediating communication between the gut and brain. Furthermore, SCFAs serve as signaling molecules throughout the body to activate many types of cells.

One dietary strategy for modulating the microbiota is the consumption of dietary fiber and prebiotics that can be metabolized by microbes in the GI tract. Human alimentary enzymes are unable to digest most complex carbohydrates and plant polysaccharides, which are instead metabolized by microbes to generate SCFAs, including acetate, propionate, and butyrate [212,213].

Prebiotic fermentation in the gut often leads to the co-production of SCFAs and gases. Excess gas production can be a potential problem for individuals with functional gut disorders. Both the chemistry of prebiotics and the composition of the microbiota are relevant to gas production [214].

The benefits of SCFAs as a treatment modality have been observed for conditions such as T2DM [215], psoriasis and acne [216], and epilepsy [217]. The use of SCFAs for the treatment of multiple health conditions and diseases is therefore a promising strategy, but more research and further clinical trials are needed to determine the overall therapeutic potential of SCFAs.

8. Conclusions

A variety of factors throughout life can impact the GM and lead to dysbiosis. Disruption of the microbial balance can often derail immune signaling, weaken intestinal barriers, reduce the level of SCFAs, and increase immune and inflammatory pathways, thereby contributing to chronic systemic inflammation and neuroinflammation. Hence, these GM-related factors are likely to play a role in the development and progression of various human health conditions. Chronic diseases could arise due to changes in the GM and BGM axis over the life continuum. Nutritional modulation can restore the microbial balance and BGM axis, thus serving as a synergistic treatment with conventional therapies. A holistic approach is possible when gut health is included in the overall management of various health conditions.

However, further research in the form of randomized-control trials is needed to support the use of gut biotics, FMT, and bacterial metabolites. Moreover, there is a need to develop guidelines for standard practice in relation to targeting of the GM and the BGM axis.

Author Contributions

TH and KA contributed to the conception and drafting of this manuscript as well as revising it. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no potential conflict of interest.

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