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Review

The Role of an Altered Gut Microbiome in Parkinson's Disease: A Narrative Review

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Abstract: Parkinson's disease is a debilitating multisystemic disorder affecting both the central and peripheral nervous systems. Accumulating evidence suggests a potential interaction between gut microbiota and the pathophysiology of the disease. As a result of the degradation of dopaminergic neurons, PD patients develop motor impairments such as tremors, rigidity, and slowness of movement. These motor features are preceded by gastrointestinal issues, including constipation. Given these gastrointestinal issues, the gut has emerged as a potential modulator of the neurodegenerative cascade of PD. Several studies have been carried out to broaden our understanding of the gut–microbiota–brain axis in PD. As a result, a decrease in short-chain fatty acid synthesizing bacteria has been observed in multiple studies. Some studies, on the other hand, have shown an enrichment of mucin- and levodopa-degrading microbes. In this review, we compiled the available evidence from the literature on the bidirectional communication between the gut microbiome system and the brain in PD. We also addressed the association between dysbiosis and the clinical symptoms of PD and host–drug metabolism. Finally, we touched on some of the therapeutic interventions that may restore eubiosis and modulate the gut structure to restrain disease progression.

Keywords: Parkinson's disease; gut–brain axis; dysbiosis; metabolomics; levodopa metabolism; therapeutics; FMT; probiotics; prebiotics

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1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's [1]. It predominantly impacts the dopaminergic neurons of the substantia nigra (SN) in the midbrain region, resulting in a decline in dopamine levels and motor impairments, including resting tremors, slowness of movement, gait disturbance, rigidity, balance issues, and akinesia. PD is not only characterized by motor and cognitive impairments but also the associated non-motor and gastrointestinal (GI) symptoms that often start to markedly manifest years or decades before the classical motor features [2]. The non-motor characteristics include constipation, dry mouth, prolonged intestinal transit time, or defecation-associated dysfunctions alongside other symptoms such as sleeping disruption, olfactory dysfunction, and depression [3]. PD is thus presumed to be a multi-systemic disease, influencing both the central and peripheral nervous systems. While the disease is in its prodromal stage, most of the non-motor symptoms are overlooked. Diagnosis and treatment begin only when the motor symptoms surface; by then, more than fifty percent of the dopaminergic neurons of the SN might have been lost [4]. Ever since the end of the prologue to PD in an observational essay on the "shaky Palsy" by James Parkinson two centuries ago, investigations to detect the trigger that progresses PD have been central [5]. The intracellular deposition of alpha-synuclein aggregates, which induce cell death and neuroinflammation, is the most widely accepted theory underlying PD pathogenesis [6]. Since Lewy uncovered the eosinophilic inclusion body and established the contribution of alpha-synucleinopathy, researchers have been interested in unravelling other aspects

of the pathophysiology of PD and in highlighting the multiple factors involved in its incidence. Environmental factors such as pesticide and insecticide exposure, xenobiotic toxins, genetic predispositions, aging, disrupted dopamine metabolism, mitochondrial dysfunction, oxidative stress, and neuroinflammation all play a role in the onset of PD [7]. The connection between PD and the GI system has long been established following Braak's hypothesis [8] that non-familial forms of PD are initiated in the gut by a pathogen. Braak's hypothesis is gaining intense support, and efforts have been carried out to disclose this potential cross-talk. In PD patients, alpha-synuclein pathology has been spotted in the gut at early stages [9]. In addition, imaging studies have revealed that in some cases of pathology, PD may propagate in the gut and spread to the brain [10]. In line with these findings, alpha-synuclein pathology migrated from the gut to the brain upon the injection of alpha-synuclein fibrils into the GITs of mice [11]. Large epidemiological studies have consistently found that people who had complete truncal vagotomies decades ago were less likely to develop PD later in life [9]. An imbalance in the gut's microbial profile may thus lead to increased susceptibility to PD. The overarching aim of this review is to gain more insights into the role of dysbiosis in the emergence of PD and its potential to serve as a biomarker for early diagnosis and treatment manipulation to slow down the progression of the disease.

2. Gut–Microbiota–Brain Axis

Ever since the establishment of Braak's hypothesis that synucleinopathy may propagate in the enteric nerves of the gut before ascending to the brain via the vagus nerve and given the early GI symptoms experienced in patients with PD, researchers have been shedding light on the role the gut microbiota plays in PD pathogenesis; hence, the term "gut-brain-axis" has emerged [12]. The microbiome consists of bacteria, viruses, fungi, archaea, protozoa, and bacteriophages. Microbial communities differ in composition and diversity depending on where they are located [4]. The human gut is home to microbial organisms, the majority of which encode more unique genes than the human genome. Unless there is a noticeable change in dietary habits, the gut microbial diversity remains mostly stable in an individual through adulthood. A dynamic shift in the gut microbial environment points towards a deteriorating immune system and its associated health consequences [13]. Emerging evidence suggests bidirectional communication between the GI tract and the brain via the central vagal nerve and systemic metabolic routes. Similarly, microbiota–gut–brain bidirectional interactions take place through neuronal, immunomodulatory, humoral, and endocrine networks [14]. It is noteworthy that the ENS innervates the GI system, and its proximity to the intestinal lumen creates an opportunity for a remarkable connection with gut microbiota. Therefore, the gut–brain axis is made up of three hubs: the brain connectome, the gut connectome, and its microbiome (Figure 1). All the hubs communicate with each other via bidirectional connections with multiple feedback loops, creating a non-linear system [15], while the CNS can directly impact the function and composition of the gut microbiota through the autonomic nervous system [16].

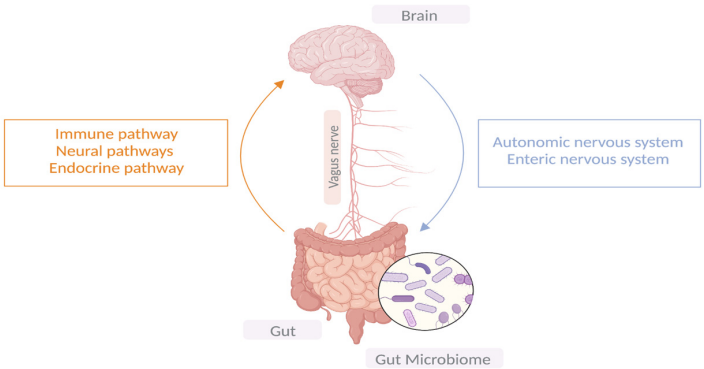

Figure 1. The bidirectional communication between the central nervous system and the GIT.

3. Gut Microbiota Disparities in PD Patients vs. Controls

Several studies have been performed in diverse populations worldwide. These studies have followed different methodologies; some employed untargeted sequencing techniques (shotgun metagenomics); others relied on a targeted approach and sequenced the 16S rRNA region; and others went for a more classical approach and performed qPCR in an effort to dissect the relative abundance of bacterial taxa in patients with PD compared to their healthy counterparts [4]. Disparities at the microbial level have been reported between PD patients and healthy controls. In 2015, researchers in Finland analyzed the fecal microbiome of 72 PD patients and 72 control subjects by pyrosequencing the V1–V3 regions of the bacterial 16S rRNA gene. Their results showed that the prevalence of *Prevotellaceae* in PD patients decreased by 77.6% as compared with the controls. Furthermore, a logistic regression classifier based on the abundance of four bacterial families and the severity of constipation identified PD patients with 66.7% sensitivity and 90.3% specificity. In addition, the relative abundance of *Enterobacteriaceae* was positively linked to the severity of postural instability and gait difficulty [17]. In 2019, Aho and colleagues conducted another study in Finland to further differentiate the gut microbiota of PD patients and the controls. They found significant differences between microbial species in PD patients and the controls, but not between time points. The reported bacterial taxa that varied between the two groups included *Roseburia*, *Prevotella*, and *Bifidobacterium* [18]. Aho et al. further compared the bacterial composition of stable PD patients with that of those with faster disease progression. The findings showed inconsistent taxa abundance across methods and time points; however, different distributions of enterotypes and a declining abundance of *Prevotella* were observed in faster-progressing patients [18]. This study intriguingly demonstrates that some bacterial taxa might be linked to disease severity and progression. Though both studies involved a Finnish population, the outcomes were inconsistent, highlighting the dynamic nature of the gut microbiome and the several factors that shape it.

Another study was conducted in a northern German cohort in 2017 and reported significant differences between PD subjects and the controls for four bacterial families; *Lactobacillaceae* were more abundant in the PD cases. A higher abundance of *Barnesiellaceae* and *Enterococcaceae* was also observed in the PD cases in this research but not in other studies [19]. Following Hopfiner, Heintz-Buschart et al. [20] characterized the microbial taxa in PD and its prodrome, idiopathic rapid eye movement sleep behavior disorder, in comparison to healthy controls. Differentially abundant gut pathogens, such as *Akkermansia*, were present in PD subjects. Additionally, 80% of the differential gut bacterial communities in PD subjects versus the healthy controls reflected similar patterns in idiopathic rapid eye movement sleep behavior disorder [20]. In another case–control study conducted on a German cohort, Weis et al. [21] found a relative decrease in the bacterial taxa linked to health-promoting, anti-inflammatory, and neuroprotective effects, such as *Faecalibacterium* and *Fusicatenibacter*. Both taxa were less abundant in PD patients, along with increased levels of the fecal inflammation marker calprotectin. Furthermore, the *Clostridiales* family XI and their affiliated members were found to be overrepresented in PD patients. Interestingly, Weis et al. took a step forward and investigated the potential impact of PD medications (i.e., Levodopa and Entacapone) on the gut microbiota composition. The relative representation of the microbial genera *Peptoniphilus*, *Finegoldia*, *Faecalibacterium*, *Fusicatenibacter*, *Anaerococcus*, *Bifidobacterium*, *Enterococcus*, and *Ruminococcus* were markedly influenced by the PD medications [21]. Weis and colleagues captivatingly brought up the host microbiome–drug interaction in PD patients and the potential influence of PD medications on the gut microbiome, which needs to be addressed in future research.

Similar studies were performed across other populations in efforts to identify disease-specific bacteria and deepen our understanding of the role of altered gut microbiota in PD pathogenesis. In the US, Keshavarzian, A. et al. [22] have investigated the colonic bacteria in both PD and control subjects. Their research showed that putative, "anti-inflammatory" butyrate-producing bacteria from the genera *Blautia*, *Coprococcus*, and *Roseburia* were significantly less abundant in the feces of PD patients than the controls, while putative

"proinflammatory" proteobacteria of the genus *Ralstonia* were significantly more abundant in the mucosa of the PD subjects than in the controls. Bacteria from the genus *Faecalibacterium* were significantly more abundant in the mucosa of the controls than the PD subjects. In 2017, researchers in the US found a significantly disrupted abundance of *Bifidobacteriaceae*, *Christensenellaceae*, *Tissierellaceae*, *Lachnospiraceae*, *Lactobacillaceae*, *Pasteurellaceae*, and *Verrucomicrobiaceae* families among PD patients as compared to the controls [23].

In 2018, a case–control study was conducted to explore the fecal microbiota composition in Chinese PD patients. The structure and richness of the fecal microbiota varied between PD patients and healthy controls. The genera *Clostridium IV*, *Aquabacterium*, *Holdemania*, *Sphingomonas*, *Clostridium XVIII*, *Butyricicoccus*, and *Anaerotruncus* were overabundant in PD patients [24], while in northeast China, Li et al. documented a remarkably altered abundance in various taxa in PD cases compared to the controls, and an elevation in *Akkermansia* and a decrease in *Lactobacillus* in the PD patients were observed [25]. Studies have continued to emerge in different regions to decipher the interplay between gut microbiota and neurodegeneration in PD. In a Russian population, Petrov et al. [26] analyzed the gut microbiota of people with PD and healthy controls using the method of high throughput 16S rRNA sequencing of bacterial genomes. The findings in the patients with PD revealed a reduced content of *Dorea*, *Bacteroides*, *Prevotella*, *Faecalibacterium*, *Bacteroides massiliensis*, *Stoquefichusmassiliensis*, *Bacteroides coprocola*, *Blautiaglucerasea*, *Dorealongicatena*, *Bacteroides dorei*, *Bacteroides plebeus*, *Prevotella copri*, *Coprococcuseutactus*, and *Ruminococcuscallidus*, while a higher abundance of *Christensenella*, *Catabacter*, *Lactobacillus*, *Oscillospira*, *Bifidobacterium*, *Christensenellaminuta*, *Catabacterhongkongensis*, *Lactobacillus mucosae*, *Ruminococcus bromii*, and *Papillibactercinnamivorans* was observed [26]. Data on the microbiota composition of Italian PD patients were also described. The PD patients were enriched with the *Lactobacillaceae*, *Enterobacteriaceae*, and *Enterococcaceae* families compared to the healthy controls, while *Lachnospiraceae* were significantly lowered [27].

Interestingly, a large-scale metagenomic study adopting a high taxonomic resolution was recently conducted to discern the role of the gut microbiome in PD. Wallen et al.'s results aligned with the existing literature and resolved the inconsistencies imposed by previous studies [28]. The species included *Blautia*, *Faecalibacterium*, *Fusicatenibacter*, *Roseburia*, and *Ruminococcus*, which are reduced in PD, and *Bifidobacterium*, *Hungatella*, *Lactobacillus*, *Methanobrevibacter*, and *Porphyromonas*, which are elevated in PD [2,29,30]. *Prevotella* has been reported as being depleted in PD by some [17,26] and as increased by others [23,31]. At the species level, *Prevotella copri* was decreased, and the pathogenic species of *Prevotella* were increased as a group, confirming the seemingly contradictory reports on *Prevotella*. Although most studies report elevated *Akkermansia* in PD patients, Wallen and colleagues described it as a "conundrum", as they did not detect a statistically significant trend for *Akkermansia* at the genus or species level in their southern US cohort, suggesting a geographic effect [28]. This finding intriguingly emphasizes that the gut microbiome is influenced by geographic locations and that populations living in different areas might be carrying unique bacterial fingerprints.

In a meta-analysis study of five 16S rRNA gene sequencing datasets, Nishiwaki et al. reported that intestinal mucin layer-degrading *Akkermansia* is elevated and that short-chain fatty acid-producing *Roseburia* and *Faecalibacterium* are decreased in PD across countries [29]. Extending the work of Nishiwaki et al., Romano and colleagues conducted another meta-analysis study of ten currently available 16S microbiome datasets to further investigate whether common alterations in the gut microbiota of PD patients exist across cohorts. The enrichment of the genera *Lactobacillus*, *Akkermansia*, and *Bifidobacterium* and the depletion of bacteria affiliated with the *Lachnospiraceae* family and the *Faecalibacterium genus* were documented [2]. Several studies have therefore capitalized on the changes in the microbial profile in patients with PD; however, extensive research is required to identify those disease-specific bacteria that might serve as robust markers to slow the progression of the disease.

4. Dysbiosis and PD Clinical Features

With growing evidence implicating the gut in PD pathogenesis and a growing appreciation for the role of gut microbiota in PD and other chronic diseases, there has been an upward trend in decoding the interplay between gut microbiota composition and PD clinical properties. Several studies demonstrated an association between dysbiosis and (1) intestinal inflammation and barrier dysfunction, (2) disease duration, (3) motor symptoms, and (4) non-motor symptoms, which is consistent with the current findings.

4.1. Microbiota Associated with Barrier Dysfunction and Gut Intestinal Inflammation

The GI tract is lined with an intestinal mucosa, which serves as a physical and immunological barrier between the environment and the internal host. This mucosa surrounds the blood circulation, which is semipermeable and crucial for nutrient uptake [4]. Microorganisms inhabiting the gut alongside their metabolic by-products are the major factors that contribute to an impaired intestinal barrier and hyperpermeability through a metabolic profile shift induced by dysbiosis, bringing about the so-called "leaky gut" and inflammation. When thrown off balance, gut-related pathogens can alter the tight junction, disrupt the permeability, and relocate via Peyer's patches [32]. This dysbiosis and increased permeability trigger, in turn, an intestinal inflammatory response and the secretion of proinflammatory markers that may penetrate the blood–brain barrier (BBB) and act on neurons and glial cells, eliciting neuroinflammation and cell death. This has been hypothesized to be associated with lowered levels of short-chain fatty acids (SCFA), signaling molecules that play a significant role in sustaining the integrity of the colonic epithelium [2]. SCFAs also have immunomodulatory functions and provoke anti-inflammatory activity via increasing and/or activating regulatory T cells [33]. A low abundance of SCFA-producing bacteria among PD patients can explain the decreased levels of SCFAs. *Prevotella*, *Faecalibacterium*, *Blautia*, and *Roseburia* were found to be depleted in PD subjects across multiple studies [18,23,34–36], whereas *Enterococcaceae* were overrepresented; *Enterococcaceae* are presumed to possibly lower the production of SCFA and secrete endotoxins and neurotoxins that promote intestinal inflammation [4]. This decreased abundance of SCFA-producing bacteria may further generate a neuroinflammatory response, which subsequently leads to the recurrent gastrointestinal symptoms affecting patients with PD. The phylum *Verrucomicrobia* (*Akkermansia*) has also been widely reported to be remarkably present in PD patients in various studies [23,37,38]. *Akkermansia* feeds on the intestinal mucin and degrades it into SCFA acetate, a substrate for other crucial bacteria to synthesize butyrate, which is an energy source for epithelial cells of the gut [39]. Additionally, *Akkermansia* enhances mucosal integrity and regulates the immune system. If the intestinal epithelium fails to compensate for the mucin utilized by *Akkermansia*, detrimental effects such as leaky gut and inflammation will arise [4]. In addition to the deficiency in SCFA-generating bacteria with anti-inflammatory properties in PD patients, an increased abundance of proinflammatory pathobionts of the phylum Proteobacteria was reported in PD patients [22]. Dysbiosis may thus result in a proinflammatory status. This triggered local inflammation could be linked to alpha-synucleinopathy. Dysbiosis and exposure to bacterial endotoxin, according to Forsyth et al. [32], may promote alpha-synuclein misfolding by inducing GI inflammation and hyperpermeability in PD patients. Together, these observations highlight the fact that dysbiosis disrupts the integrity of the GIT, eliciting an immune reaction that triggers the neurovegetative cascade of PD.

4.2. Duration of Disease, Motor Symptoms, and Associated Microbiota

Various studies have reported a link between the abundance of certain bacterial taxa and disease duration. Keshavarzian et al. [22] proposed that PD duration increases the abundance of the phylum *Proteobacteria* while decreasing the abundance of *Firmicutes*. Keshavarzian and colleagues, with findings that were consistent with those of another study by Hill-Burns et al., reported a negative correlation between *Lachnospiraceae* and duration [23]. Later, Barichella et al. discovered that the duration of the disease influenced

the gut microbiota, with enriched levels of *Lachnospiraceae* and a co-abundant genus *Akkermansia* [40]. Researchers have continued to unfold this potential association between gut commensals and PD duration. In 2015, Hasegawa et al. suggested that an elevated level in the *Lactobacillus gasseri* subgroup may predict disease duration in PD [41]. Intriguingly, the microbial composition at an early disease onset might be different to that at a late onset. Lin et al. observed that *Pasteurellaceae*, *Alcaligenaceae*, *and Fusobacteria* were more abundant in the early onset of PD, whereas *Comamonas* and *Anaerotruncus* were present in the late onset of the disease [42]. Similarly, Hill-Burns described an increased *Ruminococcaceae* in patients with the disease for more than ten years, unlike patients within the first ten years of the disease who showed less *Ruminococcaceae* abundance [23]. In conjunction with the currently known research, the gut commensals may be used as markers to detect the disease stage, as each stage might present its own unique microbial makeup.

Studies have also investigated the variation in microbial patterns with respect to motor symptoms experienced by PD patients. For example, particular gut-related pathogens, such as *Aquabacterium*, *Peptococcus*, and *Sphingomonas*, have been found to be associated with motor complications in PD [24]. Microbiota signatures may also discriminate between tremor-dominant and non-tremor PD patients. In tremor-dominant subjects, *Roseburia* [42], *Flavobacterium*, *Bacteroidia*, *Propionibacterium*, *and Alcaligenaceae* [43] are abundant, while *Leptotrichia* [42], *Clostridium*, *Verrucomicrobia*, *and Akkermansia* [43] are abundant in non-tremor PD subjects. A decreased abundance of the family *Ruminococcaceae* was noted in PD patients with tremors [21]. Bacteria associated with other motor difficulties have also been observed. *Lactobacillaceae* [40] and *Enterobacteriaceae* [17,27,42] are associated with postural instability and gait disturbance in PD, but there is also a decreased representation of *Lachnospiraceae* [40]. *Prevotella* is another promising bacterial marker that has been extensively studied in correlation with PD clinical phenotypes as well as disease progression. Several studies have shown a decreased abundance of *Prevotella* in PD patients with postural instability and gait difficulty compared to the controls [17,18,27,44]. Although several studies attribute the clinical characteristics of PD to a deviated microbial profile, future research is warranted to provide a mechanistic interpretation and to enhance our understanding of the gut microbiota and brain interactions.

4.3. Microbiota and Non-Motor Symptoms

The prodromal non-motor features, such as anosmia, depression, sleep disorders, and constipation, have been linked to an altered gut microbiota. According to Qian et al. [24] a decrease in *Bifidobacterium* abundance is linked to depression. While Barichella et al. [40] proposed a possible link between intellectual impairment and an increased abundance of *Lactobacilli* and a decreased abundance of *Lachnospiraceae.* In a more recent study, Ren et al. assessed cognitive decline using the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) questionnaires. The genera *Alistipes* and *Odoribatcer* were found to be negatively correlated with MoCA scores. *Barnesiella* is negatively associated with MMSE scores. *Butyricimonas* have been negatively associated with MMSE and MoCA scores. The genus *Blautia* of the family *Lachnospiraceae* was noted to be depleted in patients with mild cognitive impairment, whereas an enriched abundance of the families *Rikenellaceae* and *Ruminococcaceae* was reported [45]. Constipation is presumed to be one of the most common GI-associated symptoms and is reported in approximately 60% of patients with PD [4]. Research has indicated that dysbiosis may contribute to GI dysfunction and constipation at an early stage of PD pathogenesis, with an increase in *Lactobacillaceae* [30], *Verrucomicrobiaceae*, *Bradyrhizobiaceae* [17], *Bifidobacterium* [46], and *Akkermansia* [20,37,46]. *Akkermansia* has been associated with slow transit time [20,46], firmness of stool [37], and constipation severity [36]. The association between a deviated gut microbiota and the non-motor symptoms characterizing PD is becoming more evident, and these findings should open new avenues for research to better understand the exact mechanisms by which the gut bacteria contribute to PD-associated symptoms.

5. Metabolic Features in PD

The functional implications of these alterations concerning microbiota–host interactions and PD pathology are not yet fully understood. Changes in the metabolites in the feces and serum/plasma, as well as inflammatory markers, have been linked to dysbiosis [18,37]. Nevertheless, the shortlisting of the relevant metabolites and affected pathways has been challenging and discordant among the studies, except for the reproducible findings of lowered fecal SCFA levels in PD [47]. With the spiraling popularity of multi-omics strategies, endeavors have been made to investigate the metabolome–microbiome interactions and associated pathways that might be involved in PD pathophysiology.

Some studies went deeper and proposed a link between the fecal microbiota abundances and changes in amino acid metabolites [37], lipids, sulfur metabolism, bile acids [48], and SCFAs [49] in serum/plasma and the alterations of lipids, vitamins, amino acids, SCFAs, and other organic compounds in the feces of PD patients [50]. Given the lowered abundance of SCFA-generating bacteria in PD patients, acetate, propionate, and butyrate, alongside other SCFAs, were found to be decreased [51]. These molecules are endowed with anti-inflammatory activities and participate in orchestrating the function of the ENS and in enhancing gastrointestinal integrity and motility [52]. Pereira et al. used a mummichog approach to detect serum metabolite variations in PD, as well as their functional significance on over 20 pathways. The metabolic differences included the carnitine shuttle, vitamin E metabolism, glycerophospholipids, sphingolipids, fatty acids, and aminoacyl-tRNA biosynthesis [50]. A distorted pattern in sphingolipid metabolism may refer to a major shift in cell signaling and regulation. According to the literature, sphingolipid dysregulation is associated with alpha-synucleinopathy [43,53], changes in lysosomal metabolism, and mitochondrial metabolism in PD. Other metabolic and lipidomic studies have shown distortions in ceramides, sphingosine, and sphingosine-1-phosphate in PD [54,55]. Changes linked to glycerophospholipid metabolism also stood out [50]. In their review, Rodriguez-Cuenca et al. [56] referred to glycerophospholipids and sphingolipids as the "yin and yang" of lipotoxicity in metabolic diseases. Dysregulated lipid metabolism is therefore speculated to be one of the underlying pathophysiologies in PD.

Some studies have further investigated the association between bacterial taxa and metabolite features in PD. Pereira et al. [50], for example, reported a positive correlation between both enriched taxa (*Lactobacillus*, *Akkermansia*, *Bifidobacteriaceae*, *Lactobacillaceae*, *Verrucomicrobiaceae*, and *Verrucomicrobia*) and underrepresented taxa (*Roseburia* and *Pasteurellaceae*) and glycerophospholipids in PD samples. Another metabolic profiling study reported altered carnitine metabolism, fatty acid metabolism, and steroid metabolism [57]. In harmony with Shao et al., various studies have demonstrated low expression of carnitine and acylcarnitines in plasma from PD patients [58–60]. Due to insufficient oxidation, reduced long-chain acylcarnitines have been shown to be potential markers for the early diagnosis of PD [58]. The facilitation of long-chain fatty acid oxidation also influences energy metabolism. Interestingly, debilitated carnitine shuttle and vitamin E metabolism were observed in the serum from frail elderly participants without PD when compared to age-matched resilient people [61]. Accordingly, flawed carnitine shuttle and vitamin E metabolism, along with fatty acids in the serum metabolome, may hint at a remarkable shift in energy metabolism during PD. PD patients were characterized by low levels of linoleic acid and oleic acid [51]. Linoleic acid is an omega-6 polyunsaturated fatty acid (PUFA) with protective effects. Its reduction might mirror an excess of oxidative stress in PD models [62]. In findings consistent with those of Vascellari et al., PD individuals have shown reduced PUFAs, including linoleic acid [63]. Furthering the previously reported metabolic changes, vitamins B3 and B5 were found to be declining in PD. Both vitamins have anti-inflammatory and antioxidant functions and protect against neurodegeneration [51]. This reduction might be attributed to the *Lachnospira*, *Pseudobutyrivibrio*, and *Roseburia* genera. Several genera of intestinal *Firmicutes* bacteria express crucial factors for the synthesis of vitamin B3 [64]. The deficiency of vitamin B5—a key precursor in coenzyme A—might give rise to an impaired citric acid cycle and therefore distorted energy levels. This outcome has been reported in

various neurodegenerative disorders including PD, Huntington's disease, and Alzheimer's disease [65], highlighting the ability of some bacterial communities to contribute to the emergence of various neurodegenerative diseases, including PD.

Direct analysis of fecal metabolites in PD showed an altered metabolism of several amino acids, such as phenylalanine, leucine, and isoleucine [51]. A recent study showed that the levels of phenylalanine were increased in the plasma of PD subjects [59]. Other work has reported that amino acid-fermenting bacteria could modulate the expression of amino acids in the GIT [66,67] and that altered amino acid levels may reflect changes in energy metabolism [68]. Notably, a significant reduction in the glutamic acid derivative pyroglutamic acid was revealed among PD patients. Glutamic acid is a neurotransmitter involved in PD pathogenesis [69]. The results concerning the levels of glutamic acid associated with PD are rather incongruous; some studies have suggested that a decline in glutamic acid, a precursor to glutathione, may reflect an increase in oxidative stress and disease progression [70]. It is noteworthy that glutathione is a compelling antioxidant that neutralizes neurotoxins, preventing PD and other neurotoxic events. However, in response to glutamate-induced excitotoxicity, glial cells become impaired and unable to reuptake or respond to glutamate [71].

Dysbiosis appears to have a significant impact on overall homeostasis. It causes significant metabolic deviations in PD patients, resulting in impaired lipid metabolism, energy metabolism, vitamin metabolism, inflammation, and gastrointestinal dysfunctions. These modifications may precede the classical motor features defining PD; therefore, gut-related candidate biomarkers are valuable and more accessible for early PD diagnosis. Studying changes in the gut will provide additional insights into novel therapeutic strategies for the debilitating disease.

6. Gut Microbiome and Levodopa Metabolism

Our knowledge of the role of the human gut microbiome in therapeutic outcomes continues to emerge. There is accumulating evidence supporting the existence of complex gut microbial interactions with the levodopa (LD) treatment response. Administering broad-spectrum antibiotics ameliorates LD therapy, postulating the effect of gut microbiota on drug efficacy [3,72]. The commensal microbiota residing in the human gut encodes various enzymes that may chemically modify systemic and orally administered drugs; such modifications can cause activation, inactivation, toxification, and poor bioavailability [73]. LD is a dopamine replacement agent for the treatment of PD and is co-administered with carbidopa. LD can be administered via two routes: oral inhalation or infusion [74].

Recently, researchers have been eager to demonstrate drug–gut microbiota interactions. Lubomski et al. have checked the effect of levodopa-carbidopa intestinal gel (LCIG) on the microbiome structure in PD subjects. The results revealed that alpha diversity was not related to LD consumption because it was not reflected in various alpha diversity indices [36]. This finding is supported by the fact that alpha diversity does not significantly vary between PD patients and healthy controls [75]; thus, it may not serve as an efficient microbiota marker in PD. Conversely, the microbial beta diversity was significantly different, suggesting that LD may influence the gut microbiota community structure. In contrast, LCIG had significantly different alpha and beta diversities when compared to levodopa-naïve controls, probably owing to its more disruptive and direct nature. LCIG may alter the chemical environment of the gut due to its acidic properties (~pH 6.0), leading to an overabundance of *Escherichia/Shigella*. Given their tolerance for acidic conditions, these bacteria may further give rise to stomach insults and gut inflammation [36]. Research on the effect of LCIG on PD patients is still limited, and more studies on its impact on the homeostatic nature of the gut microbiota are needed for more conclusive results.

Similar work by Melis et al. showed significant differences associated with LD and LCIG administration. Correcting for major confounders, they reported an overrepresentation of the *Enterobacteriaceae* family and the *Escherichia* and *Serratia* genera in a direct comparison between the LCIG and LD cohorts [76]. Accordingly, an overabundance of the

Enterobacteriaceae species has previously been highlighted in the literature among patients with PD [25,47]. *Enterobacteriaceae* are potential pathogens whose blooming might be detrimental to the fermentation of lactic acid and endotoxin release [77]. LCIG, therefore, may have a more harmful impact on gut microbiota composition due to the higher intestinal biodisponibility of LD as it overcomes gastric transit [76]. Intriguingly, the increase in *Enterobacteriaceae* has not been addressed directly in correlation with LD or LCIG; however, it has been linked to GIT inflammation, which might be coupled with a local mechanical effect of the continuous infusion through the percutaneous gastrojejunostomy or with the potentially injurious effect of the infusion gel within LCIG [76]. Furthermore, when compared to the naive group, short-chain fatty acid (SCFA)-producing bacteria were reduced in both the LD and LCIG groups. Though these findings did not show significance after correction, further studies involving a larger sample size are warranted to tease out the impact of LD on SCFA-producing bacteria. These signaling molecules play a crucial role in gut health. Their lack increases inflammation, the risk of alpha-synuclein deposition in the GIT, and microglial activation [78].

Furthering previous findings that reported a lower abundance of *Prevotellaceae* in advanced PD, Bedarf et al. reported significantly diminished *Prevotellacopri* levels in early-stage PD patients [79]. As mentioned above, SCFAs (e.g., butyrate) are produced by *Prevotella*, and their reduction might contribute to intestinal barrier leakiness and disrupted immune functions in PD pathogenesis. It is worth noting that the intake of MAO inhibitors, amantadine, or a dopamine agonist had no impact on either taxon abundance or microbial functions [10]. Conversely, another study later revealed that different PD medications independently led to distinct microbial footprints in PD patients [23]. Given the multiple medications prescribed for patients with PD, future endeavors must address this limitation to better understand the independent effect of PD medications on gut microbiota.

A study by Palacios et al. has also looked into the microbial signatures in PD patients and reported a marginally lower abundance of *Clostridium* group IV. With respect to the association between LD use and the abundance of specific commensals, Palacios et al. did not identify any taxa remarkably associated with LD use, but preliminary findings suggested a correlation between *Clostridium* cluster IV and a short-term motor symptom response to LD [80]. This finding, however, should be revisited in larger cohorts involving a control group to delineate potential correlations.

Cosma-Grigorov A. et al. provided further evidence for disrupted abundances in the gut microbiota of PD patients [35]. The most consistently descended taxon in PD subjects was *Faecalibacterium*, which is consistent with previously published data [22,47]. *Faecalibacterium* is an SCFA-generating organism with anti-inflammatory activity [21]. In parallel with Cosma-Grigorov A. et al.'s work, Weis et al. showed a significantly decreased abundance of *Faecalibacterium* in PD patients. The reduction in this genus was coupled with entacapone treatment, which is compatible with previously reported findings [22,47]. Similarly, LD-treated patients displayed a reduced abundance of *Faecalibacterium.* A previous review by Pisanu et al. postulated that LD intake induces neuroinflammation [81]. Hence, studying the influence of LD on anti-inflammatory bacterial genera such as *Faecalibacterium* is merited to better understand the possible impact of LD on neuroinflammatory markers. According to Unger et al. and Hopfner et al. [19,47]. the family *Enterococcaceae* was not found to be different in abundance for the overall comparison of the control group and PD patients; it was significantly increased in PD patients treated with LD or entacapone. These findings put LD metabolism into question as the affiliated genus (*E. faecalis*) was described to decarboxylate LD into active dopamine in the gut, blocking its migration to the brain in vivo [73]. This means that PD patients with a particular taxon may not get enough LD and therefore they will be more susceptible to progressive PD.

Van Kessel and colleagues went deeper and evaluated the effect of PD drugs on the levels of the bacterial tyrosine decarboxylase (*tdc*) gene, which regulates the breakdown of LD in the gut [82]. They demonstrated that the increase in *tdc* gene abundance was 2.6-fold higher in PD patients compared to the controls [82]. However, no significant association was

reported between the LD dosage and the *tdc* gene abundance, unlike previous findings that showed a correlation between microbial metabolism and LD availability in rats [83]. One possible explanation for this discrepancy, as stated by van Kessel et al., is the relatively low proportion of high levodopa dosages in the recent study. Using generalized linear models, Van Kessel and colleagues showed that, alongside entacapone, other anti-PD medicaments (i.e., rasagiline and pramipexole) may influence gut bacterial *tdc* gene abundance. Another study checked only entacapone, demonstrating that it contributed to fecal *tdc* abundance and significantly increased *Enterococcus* abundance among other genera in PD patients [21]. The effect of PD medications on the gut microbiome seems to vary; thus, the independent effect of PD pharmaceuticals should be studied to ensure that patients are on the needed and most efficient treatment plan.

To further decipher the molecular mechanisms by which gut microbiota interfere with LD treatment, Maini Rekdal et al. [73] applied chemical knowledge to an interdisciplinary approach to propose the major pathway for gut microbial LD metabolism. They found that LD is converted to dopamine by a pyridoxal phosphate-dependent tyrosine decarboxylase found mainly in *Enterococcus faecalis.* This is followed by the dehydroxylation of dopamine to *m*-tyramine by a molybdenum-dependent dehydroxylase found mainly in *Eggerthella lenta.* Maini Rekdal et al. further investigated the influence of carbidopa on LD decarboxylation by *E. faecalis.* Carbidopa was not efficacious in PD patients with complex gut microbiotas, meaning that it does not terminate microbial LD metabolism but rather inhibits AADC over tyrosine decarboxylases in vivo. The revealing of the potential role of *E. faecalis* and *E. lenta* enzymes in predicting LD metabolism by complex gut microbiotas reflects the possibility of manipulating bacterial tyrosine decarboxylases and potential molecular pathways in an attempt to enhance LD bioavailability in PD patients. To elaborate, Maini Rekdal and colleagues identified a selective inhibitor of gut bacterial LD decarboxylation, named (*S*)-α-fluoromethyltyrosine (AFMT), to stop LD decarboxylation by tyrosine decarboxylase and *E. faecalis* as well as complex gut microbiota samples from PD patients. As a result, co-administering AFMT with LD and carbidopa to mice colonized with *E. faecalis* increased the peak serum concentration of LD [73]. This decarboxylation of LD by *E. faecalis* mirrors host–drug metabolism (i.e., pharmacomicrobiomics) and the way that it contributes to drug availability and interindividual variation in efficacy.

These findings, taken together, display the bidirectional effect of gut microbiota and LD; they further pave the way for future research aiming to disentangle gut microbiota contributions to LD metabolism in the effort to: (1) discover predictive biomarkers for LD metabolism and (2) identify actionable therapeutics that target host and gut microbial drug metabolism to grant patients a more tailored treatment plan based on their needs.

7. Challenges and Limitations of Current Studies

While a growing body of evidence is becoming more and more accessible with regard to the potential implication of the gut–microbiota–brain axis in PD pathogenesis, several challenges are encountered in this field. One of these challenges is that the currently available literature is not applicable to all other PD populations owing to the inconsistent results across studies. Inconsistencies might arise from various factors, such as study design, sequencing platforms, and data analysis approaches. Confounding factors, such as medications, comorbidities, and lifestyle behaviors, have also contributed to a heterogenous metadata; therefore, studies on the independent effects of such factors need to be questioned. To address these limitations, future studies should consider the following: (1) involving drug-naive and early-stage PD patients; (2) investigating the independent effect of PD medications and other co-administered drugs on microbiome composition; (3) standardizing the recruitment criteria and methodology workflow; (4) performing more population-based studies for which no data are available; and (5) performing cross-study comparisons to detect altered disease-specific pathways.

8. Gut Microbiota-Based Therapeutic Interventions

8.1. Fecal Microbiota Transplant (FMT)

The gut microbiome exhibits a great deal of plasticity and can be readily manipulated through a wide range of therapeutic approaches, some of which include FMT, probiotics, and prebiotics. FMT describes the process of transferring resuspended and filtered stools from a healthy donor to the patient's gut with the aim of restoring eubiosis [84]. Following the favorable outcomes of FMT in treating *Clostridium difficile* infection, researchers have become more motivated to investigate the potential of FMT as a therapeutic strategy for neurological disorders with promising preclinical and clinical data [84–86]. In terms of PD, Sampson et al. were the first to report that transplanting feces from PD patients to alpha-synuclein overexpressing mice significantly increased their motor symptoms compared to mice receiving feces from healthy human donors [87]. These findings were later verified in 2018 when Sun et al. reported an increase in motor deficits in healthy mice that received the fecal microbiota of PD mice. A decline in the striatal levels of the neurotransmitters dopamine and serotonin and their metabolites was also documented [88]. Conversely, transferring healthy fecal microbiota to PD mice has ameliorated motor features and decreased dysbiosis in other studies [89–91].

Zooming in on the microbial structure, FMT may result in eubiosis, which means that bacteria whose growth is unfavorable (e.g., *Desulfovibrio*, *Akkermansia*, and *Proteobacteria*) become depleted, whereas beneficial bacteria such as the *Bacteroidetes* and *Actinobacteria* phyla are enriched, particularly *Blautia* and *Prevotella* species [88]. Furthermore, FMT may sustain gastrointestinal health by preventing gut inflammation and boosting the integrity of the intestinal barrier [89]. FMT can therefore protect against leaky gut and local inflammation. FMT has also been shown to have a positive impact at the brain level. It reverses cognitive decline and promotes neuroprotection by decreasing alpha-synuclein expression and restoring optimal levels of striatal dopamine and serotonin [88,90,92]. At the molecular level, FMT may regulate the activation of microglia and astrocytes through modulating the TLR4/NF-κB proinflammatory pathway and decreasing the expression of GSK3β, iNOS, and IL-1β, which are presumed to be hallmarks of PD pathogenesis [84].

A few human case reports (Table 1) have investigated the potential therapeutic advantage of FMT. In a 71-year-old male with PD, Haung et al. reported that FMT enhanced regular defecation, and the patient did not experience tremors until after 2 months of the transfer [93]. Subsequent studies were conducted involving more PD subjects. Upon FMT, PD assessment tools showed a decline in constipation as well as motor and non-motor symptoms [94–96]. At the microbial level, PD patients who went through FMT showed an enrichment of *Blautia* and *Prevotella* and a decreased abundance of *Bacteroidetes* [95]. Thus, FMT is an effective method for gut microflora modulation. Despite that, several limitations of FMT need to be addressed. Side effects such as flatulence, diarrhea, hospitalization under observation, and GI pain [94,96]. should be further questioned. More studies involving a larger sample size are therefore needed for a better assessment of FMT efficacy, safety, feasibility, and long-term outcomes.

Table 1. The effects of FMT on PD patients.

Reference	Study Cohort	Donor	Recipient	Results
[93]	PD patient (Case report)	26-year-old healthy male	71-year-old PD patients	Tremors ↓ Constipation ↓ UPDRS score ↓ Alpha diversity ↑

Table 1. *Cont.*

Reference	Study Cohort	Donor	Recipient	Results
[94]	PD patients (*n* = 15)	5 healthy donors	PD patients	PSQI ↓ HAMA ↓ PDQ-39 ↓ HAMD ↓ UPDRS-III ↓ NMSS ↓
[95]	PD patients (*n* = 11)	Frozen fecal microbiota	PD patients	*Blautia* and *Prevotella* ↑ *Bacteriodetes* ↓ H and Y ↓ UPDRS ↓ NMSS ↓ Constipation ↓ PAC-QoL ↓
[96]	PD patients (*n* = 6)	2 healthy donors	PD patients	Motor symptoms ↓ Non-motor symptoms ↓ Constipation ↓

Abbreviations: UPDRS: unified Parkinson's disease rating scale; PSQI: Pittsburgh sleep quality index; HAMA: Hamilton anxiety scale; PDQ-39: Parkinson's disease questionnaire; HAMD: Hamilton depression rating scale; NMSS: non-motor symptoms questionnaire; H and Y: Hoehn and Yahr scale; patient assessment of constipation quality of life questionnaire; ↑: increase; ↓: decrease.

8.2. Probiotics

Probiotics are live microorganisms that, when administered in sufficient amounts, replenish the gut with beneficial commensal bacteria (e.g., *Lactobacilli*, *Bifidobacteria*, *and Enterococci*), which in turn provide favorable metabolic characteristics to the host [84]. Human clinical trials (Table 2) have exhibited probiotic supplementation as a potential therapeutic adjuvant for PD management. A randomized clinical trial concluded that milk with *L. casei* Shirota consumption diminished abdominal pain and improved stool consistency along with regular defecation [97], while supplementation with other probiotic strains such as *L. acidophilus* and *B. infantis* elicited an improvement in gut health in patients with PD [98]. PD patients were administered *L. acidophilus*, *L. reuteri*, *L. fermentum*, and *B. bifidum* in another randomized, double-blind, placebo-controlled clinical trial. The findings showed that probiotic consumption was associated with a reduction in the UPDRS motor score [99]. In findings that were not consistent with those of Tamtaji et al., Borzabadi et al. reported unchanged UPDRS motor scores and NMSS scores in patients on probiotics in comparison to the placebo cohort. Inflammatory markers such as IL-1, IL-8, and TNF- have been found to be lower in PD patients compared to the controls [100]. More recently, a randomized clinical trial showed that co-administering Probio-M8 (*B. animalis* subsp. *lactis* Probio M-8) with dopamine agonists resulted in the amelioration of non-motor features, such as sleep quality, cognitive dysfunction, defecation, and intestinal dysfunctions [101]. In line with the clinical data, probiotics manipulate the microbiota–gut–brain axis and serve as a complementary way to mitigate the rise of PD pathogenic properties.

8.3. Prebiotics

Prebiotics are referred to as plant fibers that act like fertilizers and stimulate the blooming of healthy gut bacteria in the host [102]. Prebiotics are found in foods such as soybeans, raw oats, unrefined wheat and barley, and non-digestible carbohydrates and oligosaccharides, including galacto-oligosaccharides (GOS), fructo-oligosaccharides (FOS), inulin, and lactulose [103]. Prebiotics sustain intestinal homeostasis via reducing pathogenic microbes, boosting lipid metabolism, limiting the susceptibility of *Clostridium difficile* infections, and alleviating GI and allergic diseases [104]. They further enhance

SCFA synthesis (i.e., acetate, propionate, and butyrate) in the gut; these are all molecules that participate in neuromodulation, anti-inflammatory functions, and modulation of the BBB [105]. Similar to probiotics, prebiotics can help manage neurological and neurodegenerative disorders. Lactulose and melibiose, for example, have ameliorated memory and cognitive capacity in AD mice [106]. Another study comprising AD rats showed that oral administration of *Marinda officinalis*-derived oligosaccharides boosted memory and learning ability and restricted plaque formation, oxidative stress, and inflammation [15]. In the context of PD, few animal studies have evaluated the influence of prebiotic supplementation. In a PD rat model, the administration of a medium derived from *L. salivarius* subsp. *salicinium* AP-32 culture decreased dopaminergic neuronal loss, motor impairments, muscle atrophy, oxidative stress, and inflammation [107]. In addition, Liu et al. recently demonstrated that the prebiotic polymannuronic acid may prevent dopaminergic neuronal loss via SCFA-mediated anti-inflammatory and anti-apoptotic mechanisms [108].

A few studies (Table 2) in PD humans investigated the effects of prebiotics. Astarloa et al. reported an improvement in constipation following the administration of wheat, pectin, and dimethylpolyoxyhexane-900 [109]. Supplementation with psyllium was significantly correlated with improved constipation [110]. A recently published study confirmed that orally administered resistant starch improved non-motor symptoms and increased butyrate levels in PD patients due to SCFA production [111]. Despite the satisfactory clinical outcomes of prebiotics in PD, more human clinical trials are recommended to delineate their long-lasting effects.

Table 2. The effects of probiotics and prebiotics on PD patients.

Reference	Probiotic/Prebiotic	Study Subjects	Duration	Results
[97]	*Lactobacillus casei* Shirota	40 PD patients	5 weeks	Improved stool consistency Reduction in bloating and abdominal pain.
[98]	*L. acidophilus* and *B. infantis*	40 PD patients	12 weeks	Reduction in bloating and abdominal pain.
[100]	*L. casei*, *L. fermentum*, *L. acidophilus*, *B. bifidum*	50 PD patients	12 weeks	Lowered gene expression of IL-1, IL-8 and TNF-α. Increase in TGF-β and PPAR-γ.
[99]	*L. acidophilus*, *L. reuteri*, *L. fermentum*, and *Bifidobacterium bifidum*	60 PD patients	12 weeks	Lowered UPDRS score. Decrease in hs-CRP, MDA, insulin levels, and insulin resistance. Enhancement in GSH levels and insulin sensitivity.
[112]	Xexbio (*L. acidophilus*, *L. casei*, *L. lactis*, *B. infantis* and *B. longum*)	48 PD patients	8 weeks	Improved constipation and gut motility
[113]	*L. acidophilus*, *L. reuteri*, *L. gasseri*, *L. rhamnosus*, *B. bifidum*, *B. longum*, *Enterococcus faecalis*, *E. faecium*	72 PD patients	4 weeks	Improved constipation, stool consistency, and QoL.
[101]	Probio-M8 (*B. animalis* subsp. *lactis* Probio M-8)	82 PD patients	12 weeks	Improvement in sleep quality, cognitive functions, and defecation. Manipulation of gut microbiome, lipid metabolism, SCFAs and neurotransmitters.
[109]	Dietetic fiber supplements (wheat, pectin, dimethylpolyoxyhexane-900)	19 PD patients	8 weeks	Improved constipation and motor functions. Enhanced levodopa levels.

Table 2. *Cont.*

Reference	Probiotic/Prebiotic	Study Subjects	Duration	Results
[110]	Psyllium	7 PD patients	8 weeks	Increased stool frequency and weight.
[111]	Resistant starch	57 PD patients	8 weeks	Improved non-motor symptoms. Reduced calprotectin levels. Elevated butyrate.

Abbreviations: IL-8: interleukin 8; IL-1: interleukin 1; TNF-α: tumor necrosis factor-alpha; TGF-β: transforming growth factor-beta; PPAR-γ: peroxisome proliferator-activated receptor gamma; hs-CRP: high-sensitivity C-reactive protein; MDA: malondialdehyde; GSH: glutathione; QoL: quality of life.

9. Conclusions

Extensive research has been performed speculating on the interplay between the gut and the brain in PD. The results have shown alterations in a wide range of bacterial taxa in PD patients when compared to their counterparts. A descended abundance of microbes perceived as being neuroprotective, health-promoting, and anti-inflammatory or having a preservative impact on the integrity of the gut epithelial barrier has been demonstrated. Contrary to this, an enrichment in LD-degrading bacteria has also been observed in some PD studies, reflecting the crucial role of host–drug metabolism in drug bioavailability. A plethora of pathways become disrupted because of dysbiosis; some these pathways are associated with lipid metabolism, energy metabolism, vitamin metabolism, and inflammation. Covariates were inevitable among the studies, making the road to personalized medicine more challenging. Therefore, additional population-based datasets and studies integrating different layers of omics are of the utmost importance to deal with the inconsistencies and to identify actionable biomarkers that can later be translated into clinical practice.

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