Role of the microbiome in the development of Parkinson's disease (Review)

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Abstract. Parkinson's disease (PD) is a disorder of the brain marked by the gradual loss of dopaminergic neurons in the substantia nigra, resulting in both motor and non-motor symptoms. Emerging evidence indicates that the gut microbiota plays a crucial role in the development and progression of Parkinson's disease. The present review discusses the function of the gut microbiome in PD, including its makeup, interactions with the host and putative processes that relate microbial dysbiosis to neurodegeneration. In addition, the present review discusses the possibilities of diagnostic biomarkers and microbiome-targeted therapeutics for PD. The present review synthesizes scientific literature data using a case-control approach to provide a summary of the composition of the gut microbiota in patients with PD and healthy controls. The present review includes microbiological, clinical and biomarker data in an aim to provide a better understanding of the gut-brain axis and its implications. Patients with PD have a lower microbial diversity and changes in certain bacterial communities, such as lower amounts of *Prevotellaceae* and greater amounts of *Enterobacteriaceae*. Dysbiosis can cause α-synuclein misfolding, neuroinflammation and increased intestinal permeability, potentially leading to the development of PD through the gut-brain axis. Probiotics, dietary changes and fecal microbiota transplantation all show promise for restoring microbial balance and relieving PD symptoms. Advances in metagenomics and artificial intelligence-driven analysis help to clarify microbiome-based therapies. The gut microbiota affects the gut-brain axis, neuroinflammation and α-synuclein aggregation, all of which contribute to the development of PD. Targeted microbiome therapeutics have the potential to improve illness management; however, more standardized, long-term trials are required to determine causation and therapeutic effectiveness. The present review emphasizes the relevance of personalized techniques and modern technology in microbiome research for PD.

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Abbreviations: PD, Parkinson's disease; SCFAs, short-chain fatty acids; CNS, central nervous system; GBA, gut-brain axis; MS, multiple sclerosis; α-syn, α-synuclein; ENS, enteric nervous system; LPS, lipopolysaccharide; FMT, fecal microbiota transplantation

Key words: Parkinson's disease, neuroinflammation, microbiome, gut-brain axis

Contents

1. Introduction

Review of PD. Parkinson's disease (PD), first described in 1817, is the second most prevalent neurodegenerative disorder following Alzheimer's disease, affecting 1% of individuals >60 years of age. The rising global prevalence and aging population highlight the need to understand its complexities, making it a focus of contemporary neuroscience research. This section provides a comprehensive analysis of the history, epidemiology and clinical significance of PD (1).

Parkinson's disease affects 1-2% of individuals aged ≥55 years, primarily affecting movement due to the loss of dopamine-producing neurons in the substantia nigra. This disrupts the basal ganglia network, causing motor symptoms (2). Factors such as oxidative stress, mitochondrial dysfunction and protein accumulation contribute to neuronal death. Lewy bodies, abnormal protein aggregates, are another

prominent degenerative feature of PD, causing neurodegeneration (3).

PD exhibits a wide range of motor and non-motor symptoms. The primary motor symptoms include tremors, bradykinesia, rigidity and postural instability. These are analyzed based on their progression, variation among patients, and affect daily life. Non-motor symptoms, such as cognitive dysfunction, depression, sleep disturbances, autonomic dysfunction and sensory abnormalities, sometimes manifest prior to onset of motor symptoms and significantly affect the quality of life of patients (4). PD presents a diverse range of symptoms and rates of progression, complicating diagnosis and treatment. Personalized medicine approaches, which consider genetic, molecular, and environmental factors, are crucial for improving patient outcomes.

PD is multifactorial, involving genetics, mitochondrial dysfunction, oxidative stress, neuroinflammation and gut microbiome alterations. Recent research suggests that the gut-brain axis (GBA) and mitochondrial dysfunction are interconnected in PD (5). The microbiome can influence mitochondrial function via metabolites such as short-chain fatty acids (SCFAs), and vice versa, and mitochondrial stress can affect the gut barrier and microbiome composition. Some mitochondrial disorders (e.g., POLG mutations) present with parkinsonian symptoms, which further supports the relevance (5). The exact cause of PD remains unknown, although multiple variables are considered to play a role. While the majority of PD cases are idiopathic, genetic mutations in the LRRK2, PARK7 and SNCA genes have been linked to familial PD. Certain genetic mutations and having close relatives with PD increase the risk of developing the disease. Additionally, environmental toxins and factors, such as pesticides, heavy metals and herbicides can enhance susceptibility (6).

Age is a critical risk factor for PD, with individuals aged >60 years being more likely to develop it. Notably, males are more prone to the disease than females, which may suggest sex-related differences in its pathogenesis (7). Variations in disease progression between male and female patients support the hypothesis that different pathogenic mechanisms or variations in the same mechanism may exist (8).

There is currently no reliable test available for PD; however, diagnosis relies on medical history, symptoms, neurological examination and dopamine-enhancing medication response. Misdiagnosis is common; however, neuroimaging techniques and biomarker initiatives, such as cerebrospinal fluid analysis for α-synuclein (α-syn), are being explored (3).

Although there is no cure for PD, medications help control symptoms. The most frequently used drug, levodopa, converts to dopamine in the brain. Other treatments include dopamine agonists, MAO-B inhibitors and anticholinergics (9). Surgical options, such as deep brain stimulation, involve implanting electrodes in the brain to manage motor symptoms (10). Additionally, physical therapy improves mobility, balance and flexibility, while speech therapy benefits those with speech and swallowing difficulties (11). In summary, an interdisciplinary approach to PD care involves medical treatments, lifestyle modifications, and support from family, friends, and community resources.

The human microbiome. The human microbiome is the collection of all microorganisms in the body, including bacteria, viruses, fungi and archaea, found in various sites in the body such as the gut, and is influenced by genetics, diet, lifestyle and environmental factors (12). The gut microbiome is the most complex and densely populated ecosystem in the human body, containing ~100 trillion bacteria. The predominant bacterial phyla in the gut include Firmicutes and Bacteroidetes, alongside Actinobacteria and Proteobacteria. The microbiome of each individual is unique, with marked variability observed between individuals compared to physiological changes within a single individual over time (13). The composition of the microbiome evolves dynamically during early life and can be affected by various prenatal and postnatal factors. These factors include delivery methods, breastfeeding, early use of antibiotics, and the timing and type of complementary feeding. Vaginally delivered, exclusively breastfed infants exhibit the healthiest gut microbiota, characterized by high levels of Bifidobacteria and low levels of opportunistic pathogens such as *Clostridium difficile* and *Escherichia coli* (14).

The microbiome matures during childhood and adolescence, influenced by diet, infections and the use of antibiotics. By adulthood, a stable and diverse microbiome emerges, although this remains susceptible to environmental changes. In aging populations, microbiome diversity decreases, increasing susceptibility to infections, chronic diseases and frailty (13).

The gut microbiota plays a critical role in metabolizing indigestible dietary components, such as fiber, into SCFAs, such as butyrate, acetate and propionate. SCFAs contribute to energy synthesis, immune regulation, and maintaining gut barrier integrity. The microbiome also regulates fat storage, cholesterol metabolism and vitamin synthesis, including vitamin K and several B vitamins. Emerging research highlights a strong connection between the gut microbiome and brain function, known as the GBA. Microbial metabolites, neurotransmitters (e.g., serotonin and dopamine), and immune signals influence brain development, cognition and mood (15).

A healthy gut microbiome maintains homeostasis, while dysbiosis can cause health issues. It trains the immune system to differentiate between harmless antigens and infections, preventing autoimmune reactions. Microbial fermentation produces SCFAs that regulate immune responses, reducing inflammation and promoting regulatory T-cell formation. Gut bacteria produce neurotransmitters such as serotonin, dopamine and gamma-amino butyric acid, affecting mood, cognition and behavior (14).

2. Objectives and research questions

The present study aimed to summarize the published evidence on the role of the microbiome in the pathogenesis of PD. Initial research revealed that individuals with PD have a distinct gut microbiota composition compared to healthy controls. Consequently, marked changes in the gut microbiota between patients with PD and healthy individuals need to be investigated.

Another key finding is that certain bacterial groups are associated with the severity of both motor and non-motor symptoms of PD. Therefore, the association between the gut microbiota and clinical symptoms of PD warrants

investigation. Additionally, the mechanisms through the gut microbiota influences the pathogenesis of PD need to be elucidated. Changes in the gut microbiota may lead to the development of neuroinflammation and the accumulation of α-syn, which significantly affects PD. It is equally essential to promote the discovery of novel diagnostic biomarkers and therapeutic targets, if feasible. These hypotheses and questions are discussed in the present review.

The present review article discusses the development of PD and the contribution of the microbiome to its pathology. Specifically, to conduct the review, sources from various scientific websites (such as PubMed) were reviewed, and relevant written reports were examined that highlighted the differences in the microbiome between a healthy individual and one suffering from PD. The present review compares the composition of the gut microbiome and related biological markers in patients with PD and healthy controls, using a case-control methodology. By focusing on both motor and non-motor symptoms, this approach aims to identify connections between gut microbiome dysfunction and the pathogenesis of PD. The findings were processed and reported herein. Equally important was the inclusion of other factors that contributed to the progression of the pathology of the disease in relation to the microbiome. Through the integration of microbiological, clinical data and biomarkers, this approach aims to offer a comprehensive method for researching the association between the gut microbiome and PD. In order to provide potential pathways for targeted therapeutic interventions for the microbiome, the present review discusses how gut dysbiosis may contribute to the onset and progression of PD.

3. The gut-brain axis

The theory of the GBA has garnered significant attention over recent decades, highlighting the profound impact of the gastrointestinal system on brain function and vice versa. The central nervous system (CNS), comprising the brain and spinal cord, serves as the primary control center for processing and coordinating information (16). It communicates with the gut through various pathways to regulate physiological processes and behaviors. The GBA is a bidirectional communication network that links the CNS to the gastrointestinal tract. This system integrates neurological, endocrine, and immune pathways, with the gut microbiota playing a pivotal role in modulating these connections (17). Understanding the GBA is essential for elucidating the mechanisms underlying numerous physiological processes and the pathophysiology of a wide range of conditions, including mental health disorders, neurodegenerative diseases, and gastrointestinal issues (18).

The vagus nerve serves as the primary neurological connection between the gut and the brain. It transmits sensory information from the gastrointestinal tract to the brain, while delivering motor commands from the brain to regulate gut activities. Additionally, other nerves, such as spinal afferents, contribute to this transmission (19). Hormones and neuropeptides also function as chemical messengers in the GBA. For example, ghrelin and leptin are gut-derived hormones that regulate hunger and energy balance by acting on the hypothalamus. The gut microbiota transforms dietary components into bioactive compounds, such as SCFAs, bile acids and neurotransmitter precursors. These metabolites can influence brain function by crossing the blood-brain barrier or interacting with peripheral receptors (20).

Emerging evidence suggests that the GBA may be implicated in the pathological mechanisms underlying PD. Gastrointestinal symptoms often precede motor symptoms and the diagnosis of PD, and alterations in the gut microbiota may influence the accumulation of α-syn, a hallmark of the disease (21). While the GBA presents opportunities for therapeutic intervention, further research is required to fully understand its role and develop effective treatments.

4. The microbiome and neuroinflammation

The term ‘neuroinflammation’ refers to inflammation occurring within the brain and CNS, primarily as a result of immune system activation in response to various stimuli. These stimuli may include diseases, toxins, or physical injuries. Dysbiosis, an imbalance in the gut microbiome, has been identified as a key factor in triggering or exacerbating neuroinflammation in numerous cases. Understanding the association between the gut microbiome and neuroinflammation is crucial to elucidating the mechanisms through which gut health affects brain function and contributes to neuropsychiatric and neurodegenerative diseases (22).

The immune system of the brain uses neuroinflammation as a defense mechanism against harmful stimuli. Key components include microglia, astrocytes and cytokines. Microglia are the primary immune cells, releasing pro-inflammatory cytokines to protect neurons. Astrocytes regulate inflammation and prevent damage but may promote it under certain conditions. Molecules, such as TNF-α, IL-1β and IL-6 play critical roles in immune responses. However, chronic neuroinflammation damages neurons and accelerates neurodegenerative processes (20).

The gut microbiota, a vast community of microorganisms in the body, particularly in the gut, has been linked to neuroinflammation. Dysbiosis, caused by an overgrowth of certain bacterial strains or reduced diversity of beneficial bacteria, has been associated with conditions, such as rheumatoid arthritis, colitis, hypertension and multiple sclerosis (MS). Studies using experimental autoimmune encephalomyelitis, a key animal model of MS, have highlighted the importance of microbial metabolites, such as tryptophan or SCFAs. In PD, neuroinflammation is increasingly linked to gut dysbiosis, which may exacerbate both motor and non-motor symptoms (23). Gut bacteria influence CNS physiology and inflammation through mechanisms, such as the vagus nerve, immune pathways and microbial metabolites or products, as presented in Table I. Dysbiosis disrupts these pathways, leading to neuroinflammation and changes in the permeability of the blood-brain barrier (24). Reducing neuroinflammation is vital for maintaining brain health and preventing or mitigating neurological disorders, including PD, MS, Alzheimer's disease and depression. Strategies to achieve this include dietary modifications, pharmacological treatments, alternative therapies and lifestyle changes (25).

Promoting gut health indirectly reduces neuroinflammation through the GBA. Prebiotics (e.g., fiber from fruits, vegetables and whole grains) nourish beneficial gut bacteria,

Table I. Bacteria and their association with the gut microbiome in PD.

Bacteria	Role in gut microbiome	Impact on PD	(Refs.)
Prevotellaceae	SCFA production, gut barrier integrity	Reduced in patients with PD, leading to increased intestinal permeability and inflammation	(31,33,35)
Bifidobacterium	Probiotic, supports digestion, reduces inflammation	Decreased levels in PD, associated with worsened motor and cognitive symptoms	(21,40,50)
Lactobacillus	Probiotic, maintains gut balance, produces SCFAs	Some strains are decreased, impacting gut-brain interactions and dopamine metabolism	(33,36,48)
Enterobacteriaceae	Produces endotoxins (LPS), pro-inflammatory	Increased in PD patients, contributes to neuroinflammation and α-synuclein aggregation	(14,20,26)
Akkermansia muciniphila	Mucus degradation, gut lining maintenance	Elevated in PD, excessive breakdown of gut mucus may increase inflammation	(32,44,46)
Desulfovibrio	Produces hydrogen sulfide (H_2S), disrupts gut lining	Higher levels in PD, may exacerbate gut barrier damage and motor symptoms	(15,38,50)
Ruminococcaceae	Fiber digestion, SCFA production	Decreased in PD, potentially affecting gut homeostasis and inflammation	(39,43,51)

PD, Parkinson's disease; SCFAs, short-chain fatty acids; LPS, lipopolysaccharide.

while probiotic-rich foods (e.g., yogurt, kefir and fermented vegetables) support a balanced gut microbiome. Regular cardiovascular activities, such as walking, jogging, cycling or swimming, when performed three to five times a week, also m reduce neuroinflammation (15). Chronic stress is a major contributor to neuroinflammation, as it stimulates the hypothalamic-pituitary-adrenal axis and promotes pro-inflammatory cytokine production. Therefore, a multifaceted approach involving dietary adjustments, stress reduction, regular exercise and, when necessary, pharmacological interventions, can mitigate neuroinflammation. This combined strategy protects against the development of neurodegenerative diseases and enhances overall mental well-being (24).

5. The association between α-syn protein and the microbiome

The association between the microbiome and α-syn, a protein linked to PD, has garnered significant interest within the scientific community. This connection suggests that gut health plays a crucial role in the development and progression of neurodegenerative diseases (26). The α-syn protein is typically found in neurons, although it has the capacity to misfold and aggregate into toxic clumps known as Lewy bodies, a hallmark of PD. These aggregates contribute to motor symptoms and neurodegeneration associated with the disease. The enteric nervous system (ENS), which governs gastrointestinal functions, and the brain both contain α-syn (27).

Research indicates that α-syn aggregates may form in the gut years before symptoms manifest in the brain. This raises the possibility that the causes of PD may, in some cases, originate in the gut (28). For instance, constipation, a common gastrointestinal symptom, often precedes the motor symptoms of PD by several years. According to this hypothesis, misfolded α-syn may originate in the gut, travel along the vagus nerve, and ultimately reach the brain, contributing to the neurodegeneration seen in Parkinson's disease. Dysbiosis, or an imbalance in the gut microbiome, may facilitate the misfolding of α-synuclein. Imbalances in gut bacteria can increase intestinal permeability, often referred to as a 'leaky gut', allowing bacterial endotoxins, such as lipopolysaccharide (LPS) to enter the bloodstream (26). This chronic low-grade inflammation can influence the brain via systemic and gut-specific inflammatory pathways, activating immune cells in the ENS and contributing to the production and aggregation of misfolded α-synuclein in the nervous system (29).

Research using mouse models of PD has revealed that germ-free mice exhibit a reduced α-syn aggregation and less severe motor impairments compared to mice with a normal gut microbiome. Conversely, transplanting gut microbiota from patients with PD into germ-free mice increases α-syn aggregation and exacerbates motor symptoms, indicating a potential role of specific microbial communities in disease progression (30).

SCFAs, typically anti-inflammatory, may in some cases contribute to neuroinflammation and α-syn aggregation, particularly in the context of dysbiosis. Certain Gram-negative bacteria in the gut produce LPS, a potent inflammatory agent, capable of crossing the blood-brain barrier and influencing neuroinflammation and protein misfolding (25). Furthermore, serotonin synthesis, a neurotransmitter affected in PD, is linked to tryptophan metabolism, which is modulated by the gut flora. Alterations in tryptophan metabolism may exacerbate neuroinflammation and α-syn-associated pathology (28).

On the other hand, beneficial bacteria, such as *Lactobacillus* and *Bifidobacterium*, are associated with improved gut health and reduced inflammation. These bacteria may exert neuroprotective effects by mitigating α-synuclein aggregation and promoting a balanced immune response (24).

The association between the microbiome and α-syn underscores the significance of gut health in neurodegenerative diseases, such as PD. By increasing gut permeability, activating

immune responses and generating pro-inflammatory agents, dysbiosis may facilitate the misfolding and aggregation of α-syn. Addressing gut dysbiosis through microbiome-targeted therapies may provide a promising avenue for mitigating or reversing the progression of PD.

6. Clinical evidence supporting the link between the microbiome and PD

Multiple clinical studies have consistently demonstrated significant alterations in the gut microbiota composition of patients with PD compared to that of healthy individuals. In one of the earliest comprehensive studies, Scheperjans *et al* (31) analyzed the gut microbiota of 72 patients with PD and 72 matched controls. They observed a marked reduction in the amount of *Prevotellaceae*, a family of beneficial bacteria associated with gut health, in patients with PD. *Prevotella* species produce SCFAs, which possess anti-inflammatory properties and help maintain the integrity of the gut barrier. The diminished abundance of *Prevotellaceae* in patients with PD suggests a possible connection between gut dysbiosis and the neuroinflammatory processes characteristic of the disease (32).

Keshavarzian *et al* (33) further investigated the gut microbiota of 38 patients with PD and 34 healthy controls, confirming a decrease in the number of beneficial bacteria, such as *Lactobacillus* and *Bifidobacterium*. These bacteria support gut barrier integrity and immune balance. Their study also identified an increase in the amount of *Enterobacteriaceae*, a bacterial family known to produce LPS, potent endotoxins that can induce systemic inflammation and neuroinflammation in patients with PD (33).

Several studies have highlighted the association between gut microbiota composition and the severity of motor symptoms in PD. For instance, Heintz-Buschart and Wilmes (34) analyzed 197 patients with PD and 130 controls, identifying a significant association between increased levels of *Proteobacteria*, particularly *Enterobacteriaceae*, and greater motor dysfunction. Similarly, Hill-Burns *et al* (35) reported that patients with PD with more severe motor symptoms exhibited higher levels of *Lachnospiraceae* and *Akkermansia*, suggesting that specific microbial communities may influence both disease onset and symptom progression.

The GBA, a crucial communication link between the gastrointestinal tract and the CNS, is affected by neurodegenerative disorders such as PD, with gut dysbiosis causing increased permeability.

Forsyth *et al* (26) conducted one of the first clinical studies linking PD with increased intestinal permeability. They found that patients with PD exhibited a significantly higher gut permeability, as evidenced by the presence of bacterial products in the bloodstream, compared to healthy controls. This finding underscores the potential of gut inflammation and barrier dysfunction as early contributors to the pathogenesis of PD (26).

Animal studies also support these findings. Perez-Pardo *et al* (36) demonstrated that gastrointestinal inflammation and microbiota changes in mice induced α-syn aggregation in the gut, which subsequently travelled to the brain. Although conducted in animal models, these results align with human clinical data, further strengthening the connection between gut dysbiosis, inflammation and PD (37).

PD often begins with non-motor symptoms, such as depression, cognitive decline and gastrointestinal disturbances. Sampson *et al* (38) found a significant association between gut dysbiosis and non-motor symptoms in PD, including gastrointestinal dysfunction. Their study on 103 patients with PD and 103 controls revealed a higher prevalence of pro-inflammatory bacteria, such as *Proteobacteria*, and a reduction in SCFA-producing bacteria in patients with PD (38).

Finally, the composition of the gut microbiome has been linked to cognitive decline in patients with PD. Unger *et al* (39) reported that patients with cognitive impairment had a distinct gut microbiota composition compared to those without cognitive decline, including a reduction in anti-inflammatory bacteria. This suggests that gut dysbiosis may contribute to cognitive symptoms in PD (39).

7. The composition of the microbiome in patients with PD

Patients with PD often exhibit a decrease in microbial diversity, or alpha diversity, which is linked to various diseases and dysbiosis (27). The diversity of the gut microbiome is crucial for identifying neurological disorders. Patients with PD exhibit significant changes in their gut microbiome composition, which are linked to symptoms such as neuroinflammation, intestinal barrier dysfunction and pathological lesions such as α-syn protein accumulation. The association between neurological disorders and gut microbiome diversity is not yet understood (40).

Patients with PD have a distinct gut microbiome composition, with varying levels of certain bacteria, suggesting a potential link between dysbiosis and disease severity. *Prevotellaceae* bacteria, known for producing anti-inflammatory SCFAs, such as butyrate, produce lower concentrations in patients with PD, potentially causing inflammation and increased intestinal permeability, also known as leaky gut (41).

Furthermore, pathogenic bacteria that induce inflammation, such as *Escherichia coli* and *Klebsiella*, are members of the *Enterobacteriaceae* family and produce endotoxins, such as LPS. Elevated levels of *Enterobacteriaceae* have been associated with increased inflammation in the stomach and CNS, leading to neurodegeneration in individuals with PD. Additionally, a bacterium known as *Akkermansia muciniphila* breaks down mucus and promotes the regeneration of the intestinal mucosa. While *Akkermansia* is considered beneficial, its high abundance in individuals with PD may lead to the excessive breakdown of intestinal mucus, thereby increasing intestinal barrier permeability and promoting inflammation (19).

Furthermore, hydrogen sulfide produced by *Desulfovibrio* bacteria is a gas that can damage the intestinal mucosa. Patients with PD have higher levels of these bacteria in their bodies, which is associated with gut dysbiosis and may also contribute to the worsening of motor symptoms in the disease. Furthermore, bacteria from the *Ruminococcaceae* family aid in the digestion of plant fibers and the production of SCFAs, which are essential for a healthy gut microbiota. Patients with PD often have fewer of these bacteria in their bodies, which may affect digestion and worsen intestinal inflammation (42).

Finally, the *Lactobacillaceae* family of bacteria is known for its probiotic properties, as well as its role in immune system regulation and lactic acid production. Therefore, patients with PD have significantly various levels of *Lactobacillaceae*, which may affect the balance of gut flora and inflammatory processes (40-43).

The altered composition of the gut microbiome in patients with PD raises the possibility that gut health, and the neurodegeneration characteristic of the disease are intricately linked. By worsening disease symptoms, gut dysbiosis appears to be associated with inflammation and the accumulation of α-syn, as evidenced by the increase in pathogenic microorganisms, such as *Enterobacteriaceae*, and the reduction of beneficial bacteria, such as *Prevotellaceae* (32). Understanding these changes could provide novel therapeutic avenues, including the administration of probiotics or alternative measures aimed at modulating the microbiome.

The composition of the human gut microbiome varies significantly across different populations due to cultural, dietary and geographical factors. These variations have profound implications for the development and progression of diseases, including PD. Diet is one of the most influential factors shaping the gut microbiome. Populations with diets rich in plant-based, fibber-rich foods, such as those in Mediterranean or Asian countries, tend to have higher gut microbiota diversity. Elevated levels of beneficial bacteria, such as *Bifidobacterium* and *Lactobacillus* are associated with these diets, which are linked to anti-inflammatory effects and improved gut barrier integrity (14). By contrast, Western diets, characterized by a high consumption of refined sugars, saturated fats and processed foods, are associated with reduced microbial diversity and the increased prevalence of pro-inflammatory bacteria, such as *Enterobacteriaceae*. These dietary patterns may exacerbate gut dysbiosis, a factor implicated in the pathology of PD (34). Fermented foods, a staple in a number of traditional diets (e.g., kimchi in Korea or kefir in Eastern Europe), are rich in probiotics such as *Lactobacillus*. These foods support the balance of the gut microbiota and may help mitigate dysbiosis observed in patients with PD. Cultural practices, such as fasting, which alter gut microbiota composition, also have potential therapeutic implications for PD (14). These dietary influences may partially explain why the prevalence and severity of PD vary across regions. For example, it has been suggested that Asian countries have lower prevalence rates of PD compared to Western countries, due to differences in traditional diets and lifestyle factors (40).

Geographical location significantly affects the microbiome through environmental exposures, lifestyle differences and cultural dietary preferences. Rural populations in Africa and South America have a dominant microbiome dominated by fibber-fermenting bacteria, producing essential SCFAs, such as butyrate for gut health and inflammation modulation, while urbanized populations in Europe and North America have lower levels of *Prevotella* (32).

While these patterns provide valuable insight, individual variability, genetic predispositions and confounding factors, such as the use of medications and socioeconomic status should also be considered. Future research is required to focus on cross-cultural analyses to elucidate the interactions between dietary habits, microbiome composition and the risk of developing PD.

8. Connection between the development of PD symptoms and the microbiome

Studies examining the association between the gut microbiome and the onset of PD symptoms are rapidly expanding. According to recent research, dysbiosis or alterations in the gut microbiome, may play a crucial role in the development and progression of PD symptoms. Evidence suggests that the gastrointestinal tract may be an early source of pathology in PD, with gut-related symptoms, such as constipation, sometimes manifesting years prior to the onset of motor symptoms (44).

The ENS and CNS communicate bidirectionally via the GBA, involving the vagus nerve, immune pathways and microbial metabolites. Disruptions in this communication pathway, caused by gut dysbiosis, have been linked to neuroinflammation and neurodegeneration in PD (17,19).

There is a theory suggesting that α-syn may initially accumulate in the ENS as a response to toxins from pathogenic microorganisms. The accumulated α-syn protein may then pass through the vagus nerve and reach the brain, potentially leading to neurodegeneration in PD (44). This notion is supported by the discovery of α-synopathy in the gastrointestinal tissues of patients with PD, even in the preliminary stages of the disease. At the same time, reduced levels of butyrate may render the gut less capable of maintaining a protective barrier, thus increasing intestinal permeability and facilitating the entry of bacterial endotoxins, such as LPS, into the bloodstream. These endotoxins may enter the brain and worsen the symptoms of PD by inducing neuroinflammation and neuronal death.

The vagus nerve, a direct pathway between the stomach and brain, may be involved in transmitting misfolded proteins or inflammatory signals from the stomach to the brain. Studies show that the surgical severing of the vagus nerve reduces the risk of developing PD (45). Gastrointestinal issues, such as constipation, are common in individuals with PD, thus suggesting that gut-related mechanisms may influence the early pathogenesis of the disease. In some cases, α-syn accumulation in the ENS may occur before the brain (46)

There is strong evidence to indicate that the onset and progression of PD symptoms are significantly influenced by the gut microbiota. The misfolding of α-syn, increased intestinal permeability and neuroinflammation appear to be impacted by dysbiosis in patients with PD. Restoring microbial balance through therapies has the potential to alleviate both motor and non-motor symptoms of the disease, making the GBA a promising therapeutic target. In order to fully understand the processes related to the microbiome and PD and to develop effective microbiome-based treatments, further research is warranted (47).

9. Synopsis and conclusions

The association between PD and the gut microbiome is becoming increasingly evident, as research indicates that changes in the composition of gut microbes can have a significant effect on the development and progression of the

symptoms of the disease (48). The vagus nerve, immune pathways and the production of microbial metabolites, such as SCFAs, are among the communication channels that link the gut and the CNS via the GBA (49).

Notable alterations in gut flora, known as dysbiosis, have been repeatedly reported in patients with PD (50). The amounts of beneficial bacteria, such as *Prevotellaceae*, are reduced, while potentially harmful bacteria, including *Enterobacteriaceae* and *Akkermansia muciniphila*, proliferate (51). The reduction in the amount of *Prevotellaceae* is associated with the decreased production of SCFAs, such as butyric acid, a crucial compound that maintains gut barrier integrity and possesses anti-inflammatory properties (52). The deficiency of butyric acid makes the gut more permeable, facilitating the entry of harmful compounds into circulation, such as lipopolysaccharides or bacterial endotoxins (53). These molecules can exacerbate neurodegenerative processes in the brain and induce systemic inflammation (54).

The rise in opportunistic infections due to the endotoxins of *Enterobacteriaceae* bacteria can exacerbate inflammation, potentially affecting the CNS and worsening the symptoms of PD. Increased concentrations of these bacteria are linked to more severe motor symptoms in patients with PD, highlighting their role in the progression pf the disease (22).

PD may be linked to α-syn, a misfolded protein that accumulates in the brain. Recent data suggest that this misfolding may begin in the ENS, be influenced by gut dysbiosis, and then pass through the vagus nerve to the brain. The 'intestinal origin' theory suggests microbial imbalances in the gut may cause α-syn accumulation in the brain. The presence of α-syn aggregates in the ENS and the early onset of gastrointestinal issues highlight the importance of gut health in the early development of PD (55).

This knowledge of the GBA in PD has significant therapeutic implications. Probiotics, prebiotics, dietary modifications and fecal microbiota transplantation (FMT) are some examples of microbiome-centered interventions that provide promising means for restoring microbial balance, reducing neuroinflammation and potentially alleviating symptoms of PD. Preliminary resesarch suggests that these approaches can modify the gut microbiome and improve the progression of the disease in both human and animal models (56). The increased synthesis of SCFAs and beneficial bacterial populations can be achieved through the use of probiotics and dietary fibers. This could improve gut health and potentially attenuate the inflammatory cascade associated with neurodegeneration. FMT has exhibited promise in restoring a a healthy gut microbiome, potentially correcting dysbiosis and delaying the progression of PD, despite its experimental nature (57).

In summary, the association between the gut microbiome and PD is a critical area of study that promises cutting-edge therapeutic approaches. Dysbiosis, defined as the overgrowth of pathogenic microbes and the reduction of beneficial bacteria, is considered to be a key factor in the development and progression of PD. Neuroinflammation and the accumulation of α-syn in the brain may be caused by gut imbalances via the GBA, specifically through the vagus nerve and immune pathways. Understanding these processes may lead to the development of novel therapeutic strategies aimed at shaping the gut microbiome, increasing the prospect of better control and possibly even the prevention of PD (40).

Potential therapeutic approaches. The potential of FMT as a therapeutic approach for PD has attracted increasing clinical interest. Several case studies and small-scale trials have revealed that modifying the gut microbiome may help alleviate symptoms in patients with PD, even though clinical trials are still in their preliminary stages. A 71-year-old PD patient who underwent FMT to relieve constipation, a common non-motor symptom of the disease, was the subject of a case report published by Segal *et al* (58). Notably, following the FMT procedure, the motor symptoms of the patients improved, including a reduction in rigidity and tremors, in addition to the resolution of constipation (58). Although this is an informal case, it demonstrates how promising microbiome-targeted therapies could be for PD (59).

In the study by Xue *et al* (60), 6 patients with PD underwent FMT, providing further evidence. According to the Unified PD Rating Scale, the motor functions of the patients improved following treatment, in addition to the resolution of their gastrointestinal issues. Despite the moderate scope of these trials, they provide some early evidence supporting the hypothesis that modifying the gut microbiome through FMT may have therapeutic benefits for patients with PD (60).

Numerous studies have demonstrated that by improving gut health, reducing inflammation and influencing the GBA, certain probiotics may help manage PD (59). Probiotics can assist individuals with PD by addressing gastrointestinal symptoms, including constipation, and potentially reducing some of the neuroinflammatory and neurodegenerative processes associated with the condition, although research in this area is still ongoing (56). For instance, the ability of *Lactobacillus plantarum* to improve intestinal barrier function and its anti-inflammatory properties have been well-documented. By enhancing the production of SCFAs, such as butyric acid, which has a protective effect on the gut and can reduce neuroinflammation in PD, *Lactobacillus plantarum* has shown promise in improving gastrointestinal health (61).

Studies have demonstrated that *Lactobacillus plantarum* can reduce inflammation and promote gut health, both crucial aspects of managing gastrointestinal symptoms related to PD, including constipation. Tan *et al* (56) studied patients with PD and found that probiotics containing *Lactobacillus* and *Bifidobacterium* species improved constipation and gut dysbiosis after 12 weeks. The study by Barichella *et al* (46) demonstrated that constipation in patients with PD could be alleviated by combining a fibber-rich diet with probiotics, indirectly suggesting that probiotics are beneficial in managing stomach-related symptoms.

The existing evidence suggests that probiotics, specifically strains of *Lactobacillus* and *Bifidobacterium*, may be helpful in managing the non-motor symptoms of PD, particularly gastrointestinal issues such as constipation, although more extensive clinical trials are required (31). These probiotics may also help reduce gut-derived neuroinflammation, which could impact the progression of PD. Probiotics have the potential to be a valuable complementary therapy for managing both motor and non-motor symptoms of PD, as this field of study continues to develop (46).

Advances in microbiome research have opened new avenues for personalized medicine, particularly in the context of PD. Personalized approaches aim to tailor therapies based on the unique microbiome composition of an individual, genetic predispositions and environmental factors. This strategy provides marked potential for improving treatment efficacy and reducing side-effects (62). Personalized medicine in PD also considers the interplay between medications and the gut microbiome. Drugs such as levodopa are metabolized by gut bacteria, which can influence their efficacy and side-effects. Pharmacogenomic approaches that account for these interactions could optimize treatment outcomes (35). Artificial intelligence (AI)-driven models can analyze microbiome data alongside genetic and clinical information to predict disease progression and identify optimal therapeutic strategies. These tools enable dynamic, data-driven personalization of microbiome-targeted therapies (63).

Recent advancements in microbiome research have enabled a more in-depth understanding of the intricate association between the gut microbiome and PD. Technologies such as metagenomics, metabolomics and multi-omics approaches are currently pivotal in elucidating these connections.

Metagenomics is a method that analyzes genetic material from environmental samples, including the human gut microbiome. It identifies specific microbial genes associated with PD and provides insight into functional changes in the microbiome (64). For instance, reduced SCFA production genes in patients with PD suggest an impaired anti-inflammatory response (43).

Multi-omics approaches combine metagenomics, metabolomics, transcriptomics and proteomics to create a holistic view of the GBA. These integrative studies are helping to identify causal associations between gut microbiota alterations and PD pathology. For instance, integrating metagenomics and metabolomics data has highlighted the role of *Akkermansia muciniphila* in mucosal barrier degradation and its association with increased gut permeability in PD (41).

Single-cell sequencing technologies are emerging as a tool to study the functional heterogeneity of microbial communities in the gut. By analyzing individual bacterial cells, researchers can better understand the dynamics of specific bacterial populations in patients with PD (34).

Machine learning and AI are being employed to analyze vast microbiome datasets. These tools enhance the accuracy of predictions regarding disease progression and the identification of potential therapeutic targets. For example, the AI-driven analysis of microbiome data has revealed predictive patterns of gut dysbiosis in early-stage PD (63).

Emerging technologies provide insight into the GBA and enable personalized medicine in the treatment of PD. These tools can develop microbiome-targeted interventions to address both motor and non-motor symptoms. Studies show altered gut microbiota in patients with PD, associations between microbial changes and symptoms, and indications of intestinal permeability and inflammation (50). Probiotics and FMT are examples of microbiome-targeted therapies that address gut dysbiosis and α-syn accumulation. However, further research is required to prove causal associations and the specific mechanisms influencing the microbiome (61).

Limitations and future directions. Despite the growing interest in the role of the microbiome in PD, several limitations and controversies exist that hinder the full understanding and clinical application of these findings. These challenges stem from methodological inconsistencies, technological limitations, and the complex interplay between environmental and biological factors.

Microbiome research faces challenges due to standardized methodologies, resulting in inconsistent results across studies. Variations in sample collection, storage, DNA extraction and sequencing platforms can introduce bias in microbial composition analysis (37). Disparities in sequencing technologies can yield different taxonomic and functional profiles, making it difficult to compare findings and establish universally accepted microbial markers for PD. Small sample sizes limit statistical power and generalizability, and larger, multi-centered studies are required to validate observed trends and account for demographic and geographic variability (40).

The composition of the gut microbiome is influenced by numerous factors beyond disease status, including diet, medications, age and comorbidities. For instance, anti-PD medications such as levodopa can alter the gut microbiota, confounding studies that attempt to link microbiome changes to PD pathology (35). Without proper controls, it is challenging to discern whether observed microbial alterations are a cause or consequence of PD. A key controversy in microbiome research is the difficulty in establishing causal association between dysbiosis and PD. While many studies have identified associations between specific microbial changes and disease symptoms, proving causation remains elusive. For instance, gut dysbiosis may be both a driver and a consequence of PD-related gastrointestinal dysfunction (32). Longitudinal studies and experimental models are essential for addressing this issue. The GBA involves multiple pathways, including immune signaling, neural communication and microbial metabolite production. Untangling these interconnected mechanisms poses a significant challenge. For example, while SCFAs are implicated in neuroinflammation, their exact role in PD pathology remains unclear (20).

The association between PD and gut microbiota has been studied; however, challenges remain due to the complexity of the GBA, methodological difficulties and heterogeneity of findings. Studies use various sampling strategies, sequencing technology and analytical procedures, making it difficult to understand the role of the microbiome in PD. Larger, multi-centered studies are warranted to validate reported gut microbial changes and their impact on the development of PD.

Lifestyle, medications and diet significantly influence the gut microbiota; however, it is challenging to determine whether these changes are due to food or medication or directly related to PD. The condition is highly heterogeneous, with varying symptoms, progression and pathology, rendering it difficult to identify a single PD microbiome for therapeutic intervention.

Although gut dysbiosis is commonly observed in patients with PD, it remains unclear whether these changes are a cause or an effect of the disease. Determining the exact causal association between specific microbial changes and the pathology of PD is challenging, as the gut environment may be influenced by neurodegenerative processes and disease progression (65).

Several interconnected systems, including the immune system, the vagus nerve, microbial metabolites and the ENS, are involved in the GBA. Identifying the precise processes by which the microbiome may influence the development of PD is a difficult task due to its complex nature.

Future research is required to prioritize large-scale, longitudinal cohort studies to determine the association between gut microbiome changes and PD symptoms. This approach will help determine whether gut dysbiosis precedes both motor and non-motor symptoms and whether it serves as a causal factor. Cross-sectional strategies cannot provide conclusive conclusions.

Future therapies should be personalized, as the gut microbiota varies across individuals. Probiotics and FMT specifically designed to match the microbiome profile of each patient, to maximize therapeutic effectiveness, are examples of personalized microbiome treatments. These may involve the direct provision of beneficial metabolites to reduce inflammation and promote neuroprotection, considering the role of microbial metabolites in gut-brain communication, such as bile acids and SCFAs (62,65).

Current technologies, while advanced, have their limitations. For instance, 16S rRNA sequencing provides taxonomic profiles, but lacks functional insight. Metagenomics and metabolomics offer functional data, but are costly and computationally intensive. Single-cell analysis promises higher resolution, but is still in its infancy for microbiome studies. The lack of a gold standard for microbiome analysis further complicates research efforts and impedes progress toward clinical applications (66).

Diet plays a critical role in influencing the gut microbiome, and future research should explore how specific dietary interventions, such as high-fiber diets, ketogenic diets, or anti-inflammatory diets, affect the gut microbiome to potentially delay the onset of PD. This research is still in its early stages, and larger, more thorough studies, mechanistic research and customized treatments are warranted in order to fully realize the therapeutic promise of gut-targeted therapies (61).

Human microbiome studies often face limitations due to invasive methods and ethical concerns, particularly in vulnerable populations such as patients with PD. To overcome these issues, future research should standardize protocols, conduct large-scale longitudinal cohort studies, integrate multi-omics approaches, and develop computational tools and machine learning algorithms for managing and analyzing complex datasets, as well as conducting longitudinal cohort studies (14).

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Competing interests

The authors declare that they have no competing interests.

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