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REVIEW ARTICLE

Gut dysbiosis in Parkinson's disease: A systematic review of human studies

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Abstract

Introduction: Parkinson's disease (PD) is increasingly correlated to gastrointestinal disturbances and intestinal microbiota alterations. Growing evidence suggests that shifts in gut microbial communities may influence immune activation and metabolic pathways relevant to PD.

Objective: This systematic review examines microbial changes in PD and their clinical relevance.

Methods: A systematic search of PubMed, Scopus, and Web of Science identified 819 records. After removing duplicates and screening, 521 full-text articles were evaluated. Ten studies met the inclusion criteria, focusing on human subjects and original data on gut microbiota composition, function, or modulation in PD.

Results: The microbiome profile most frequently reported in PD includes a drop in overall diversity and in bacterial taxa associated with short-chain fatty acid production, alongside a shift toward taxa commonly associated with inflammatory states (e.g., Enterobacteriaceae). Most studies reported associations between dysbiosis and motor severity, constipation, autonomic dysfunction, and neuropsychiatric symptoms. Interventions such as resistant starch supplementation and acupuncture improved microbial profiles and some clinical outcomes. Machine-learning approaches showed promising diagnostic potential based on microbial signatures.

Conclusions: Gut dysbiosis is significantly associated with PD clinical features. Although early evidence suggests potential therapeutic and diagnostic applications, methodological heterogeneity and small sample sizes highlight the need for standardized, longitudinal research.

Keywords: Parkinson's disease; Gut microbiota; Gut–brain axis; Neuroinflammation; α-synuclein; Probiotics; Fecal microbiota transplantation

1. Introduction

Parkinson's disease (PD) is a steadily progressive neurodegenerative condition classically linked to the loss of dopaminergic neurons in the substantia nigra pars compacta, which underlies core motor features including bradykinesia, resting tremor, rigidity, and postural instability. In recent decades, however, PD has been reframed as a multisystem disease with manifestations extending well beyond the motor domain.[1-4] Non-motor symptoms, including constipation, hyposmia, sleep disturbances, depression, anxiety, autonomic dysfunction, and cognitive impairment, are now considered integral components of the disease, often appearing years before motor deficits become clinically evident. This long prodromal phase has stimulated increasing interest in peripheral mechanisms that might contribute to the initiation and progression of PD.

Among peripheral systems, the gastrointestinal tract has become a focal point for research. Gastrointestinal symptoms are highly prevalent in PD, with chronic constipation representing one of the earliest and most persistent complaints.[5,6] Neuropathological evidence has identified α-synuclein deposits within the enteric nervous system, including in subjects without a clinical PD diagnosis, which aligns with the idea that disease-associated changes may begin in the gastrointestinal tract. This model is further supported by the proposed spread of misfolded α-synuclein from the gut to the central nervous system through vagal pathways, offering a rationale for the early gastrointestinal features frequently observed in PD.[7-11]

Parallel to these insights, scientific interest has increasingly shifted toward the gut microbiota, a complex microbial ecosystem essential for digestion, metabolic homeostasis, immune regulation, and the maintenance of the intestinal barrier. In recent years, the concept of gut dysbiosis, a disruption in the normal composition or function of the gut microbiota, has emerged as a key factor in the pathogenesis of systemic and neurological diseases.[12-21] Alterations in microbial populations have been shown to influence systemic inflammation, oxidative stress, production of neuroactive metabolites, and permeability of the gut barrier, all processes that may play a role in PD pathophysiology. Research conducted across different populations consistently reports specific microbial signatures in individuals with PD, including reduced levels of short-chain fatty acid (SCFA)-producing bacteria and increased abundance of pro-inflammatory taxa.

These abnormalities have been linked to both gastrointestinal and neurological manifestations, suggesting that gut dysbiosis may contribute to the disease through multiple interconnected pathways.[22-26] Growing interest in the gut–brain axis, a bidirectional communication network connecting the central nervous system and the gastrointestinal tract, has provided a biological basis for these interactions. Microbial metabolites can influence neuronal activity, immune signaling, and barrier integrity, offering plausible mechanisms through which gut dysbiosis may modulate neurodegenerative processes. As a result, microbiota-directed therapeutic approaches, including dietary modification, probiotic and prebiotic supplementation, and fecal microbiota transfer, have gained attention, although the current evidence remains preliminary and heterogeneous.[27,28]

Given the rapid expansion of research in this area, a systematic synthesis of the available studies is essential to clarify the nature of microbial alterations in PD, their clinical relevance, and their potential mechanistic implications.[29-33]

1.1. The gut microbiota and its role in human health

The intestinal microbiome is a remarkably complex and highly adaptable ecosystem composed of trillions of microbes residing in the human gastrointestinal system.[34-38] This ecosystem includes bacteria, archaea, viruses, and fungi that coexist in a finely regulated equilibrium essential for maintaining host health. Microbiota composition is highly individualized and influenced by several determinants, including host genetics, early-life microbial exposure, diet, physical activity, environmental factors, and medication use, such as antibiotics or proton pump inhibitors.[39-48] Despite this variability, several core functions of the microbiota remain consistent across individuals and are fundamental in sustaining physiological balance.[49-53] Among its primary functions, the gut microbiota contributes to the digestion and fermentation of otherwise indigestible dietary components, leading to the production of SCFA, such as acetate, propionate, and butyrate, which fuel colon epithelial cells and provide anti-inflammatory, as well as immunoregulatory actions throughout the body.[54-58] In addition to nutrient processing, the gut microbiota plays a crucial role in immune development

and tuning, shaping immune-cell responses, modulating cytokine responses, and helping maintain tolerance toward commensal microorganisms, thereby preventing inappropriate inflammatory reactions.[59-63] Another fundamental role of the microbiota is its contribution to intestinal barrier function. By modulating tight-junction proteins, mucus production, and epithelial turnover, a well-regulated microbial community helps preserve the permeability of the gastrointestinal barrier.[64-68]

Disruption of these mechanisms, often caused by dysbiosis, may increase gut permeability, a condition known as "leaky gut," which, in turn, allows the translocation of microbial products, such as lipopolysaccharides, into the bloodstream, triggering low-grade inflammation.[69-73]

Beyond the gastrointestinal tract, microbial metabolites and signaling molecules reach distant organs through circulation and neural pathways, exerting profound effects on metabolism, endocrine activity, and brain function.[74-78] The discovery of these long-range interactions has fundamentally changed the understanding of human physiology, positioning the gut microbiota as a key orchestrator of systemic homeostasis.[79-83]

1.2. Gut dysbiosis in Parkinson's disease: clinical and biological implications

Accumulating evidence indicates that people living with PD exhibit consistent and measurable alterations in their intestinal microbiota. These changes, often described as gut dysbiosis, involve shifts in both microbial composition and functionality.[84-88] One of the most widely reported findings in PD cohorts is a marked reduction of bacteria capable of producing SCFA, particularly butyrate-producing taxa, including *Faecalibacterium* and *Roseburia*. Since butyrate is crucial for supporting barrier function and promoting anti-inflammatory activity, its depletion may create a permissive environment for chronic inflammation and increased gut permeability.[89-93] Concurrently, several studies have documented a rise in inflammation-associated taxa, including members of the Enterobacteriaceae family and other Gram-negative organisms. These bacteria produce endotoxins and other inflammatory molecules that can activate the immune system at the intestinal level and throughout the body.[94-98] The resulting immune activation may contribute to enhanced cytokine production, oxidative stress, and mitochondrial dysfunction, processes strongly associated with PD pathophysiology. These microbial alterations correlate with a number of gastrointestinal symptoms frequently reported by patients with PD, such as constipation, bloating, abdominal discomfort, and altered motility.[99-103] More importantly, dysbiosis has been associated with gastrointestinal complaints and also with the intensity of motor and non-motor manifestations, including cognitive decline, anxiety, depression, and sleep disturbances. These correlations support the idea that gut microbiota changes may influence neurological function through inflammatory, metabolic, and neuroimmune pathways.[104-108]

At the biological level, microbial products such as bacterial endotoxins, altered bile acid profiles, and metabolites derived from amino acid fermentation may influence α-synuclein folding and aggregation. Increased intestinal permeability may allow these compounds to reach the systemic circulation, potentially contributing to neuroinflammation and enhancing the vulnerability of dopaminergic neurons. Although the exact temporal sequence remains under investigation, the convergence of clinical and molecular data supports a model in which gut dysbiosis may represent more than a downstream effect of PD, potentially contributing to disease evolution.[109-113]

1.3. The gut–brain axis as a mechanistic link

The gut–brain axis is a complex, tightly coordinated network linking the gastrointestinal tract and the central nervous system.[114-118] This interaction relies on multiple pathways, including the vagus nerve, the enteric nervous system, endocrine signaling, immune mediators, and microbiota-derived metabolites. Together, these mechanisms allow continuous two-way communication between the gut and the brain, thereby enabling the gastrointestinal environment to influence neural activity, behavior, and cognitive functions.[119-126]

A major element of this axis is the vagus nerve, which directly links the enteric nervous system to central autonomic nuclei. Experimental studies have shown that vagal pathways can transmit signals related to inflammation, microbial composition, and metabolic changes, influencing regions involved in motor control, mood regulation, and stress responses.[127-135] Alterations in vagal signaling have been proposed as a potential route for the propagation of misfolded α-synuclein from the gut to the brain, particularly toward the dorsal motor nucleus of the vagus.

Microbial metabolites provide another important avenue of interaction.[136-140] SCFA can modulate microglial activation, influence gene expression in neuronal cells, and regulate the permeability of the blood–brain barrier. Likewise, tryptophan metabolites derived from microbial metabolism may affect serotonin pathways, impacting mood, sleep, and gastrointestinal motility, all commonly altered in PD.

Bile acid derivatives and other microbial products can act as signaling molecules, influencing nuclear receptors

and inflammatory cascades in both peripheral tissues and the central nervous system.[141-147]

The immune pathways also play a crucial role. Dysbiosis can trigger pro-inflammatory cytokine production, activate pattern-recognition receptors, and disrupt regulatory immune networks.These immune responses can subsequently affect central inflammatory processes, contributing to microglial activation and neuronal stress.[148-157] Over time, this neuroinflammatory environment may amplify neurodegenerative cascades, particularly in individuals who already possess genetic or environmental risk factors for PD. The multifaceted nature of the gut–brain axis highlights its potential significance in understanding PD pathogenesis.[158-159] By integrating signals from microbial communities, immune responses, metabolic pathways, and neural circuits, this axis may represent a key interface through which gastrointestinal health influences neurological vulnerability. Understanding these mechanisms is essential for developing diagnostic biomarkers and designing targeted interventions that modulate gut–brain communication in PD.[160-165]

In this context, the present systematic review aims to offer additional insights into existing narrative and systematic syntheses by providing an updated and clinically oriented integration of gut microbiota alterations in PD. Specifically, we summarize recurrent microbial patterns across studies while also considering key sources of heterogeneity (e.g., study design, sampling methods, sequencing approaches, and relevant clinical variables) and, where available, their associations with motor and non-motor features. By linking microbiota signatures to clinically meaningful outcomes, this review seeks to inform future efforts toward biomarker discovery for earlier identification and risk stratification, support symptom-based patient stratification, and clarify the rationale for microbiota-targeted therapeutic strategies (dietary interventions, probiotics/prebiotics, and other emerging approaches). Ultimately, delineating consistent microbial signals and their clinical correlates may facilitate translation of descriptive findings to actionable hypotheses for clinical research and patient care.

2. Materials and methods

2.1. Protocol and registration

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines and was registered in the International Prospective Register of Systematic Reviews (CRD420251247392). The primary aim of this review is to evaluate the relationship between gut microbiota alterations and PD in human subjects. A protocol was developed prior to initiating the review process to ensure methodological transparency and reproducibility.

2.2. Search processing

A comprehensive literature search was performed across three major databases, PubMed, Scopus, and Web of Science, from January 1, 2015, to July 1, 2025. The following Boolean string was used: ("Parkinson's disease" OR "Parkinson disease" OR "PD") AND ("gut microbiota" OR "gut microbiome" OR "intestinal microbiota" OR "intestinal microbiome" OR dysbiosis OR "gut dysbiosis") AND ("neuroinflammation" OR "inflammation" OR "gut–brain axis" OR "alpha-synuclein").

2.3. Inclusion criteria

Three reviewers reviewed all relevant publications that met the following criteria: (i) only human subjects research, (ii) full text, and (iii) scientific studies evaluating the connection between gut microbiota alterations and the onset of PD. The PICOS model was used in accordance with the following steps:

- Criteria: Application in the present study;
- Population: Human subjects;
- Intervention: Evaluation of 16S rRNA sequencing and metaproteomics, microbiota therapy;
- Comparison: Control group;
- Outcome: Evaluation of the connection between gut microbiota alterations and the onset of PD;
- Study design: Randomized controlled trials, prospective observational case-control study, case series, secondary data analysis of Parkinson's Progression Markers Initiative, open-label non-randomized, multi-omics analysis, case-control study.

2.4. Exclusion criteria

The exclusion criteria were non-English-language articles, ineligible research designs, ineligible outcome measures, ineligible populations, case studies, reviews, and animal studies.

2.5. Data processing

All disagreements among reviewers regarding eligibility or extracted data were resolved through discussion until consensus was reached. The reviewers adhered to standardized extraction procedures to maintain consistency across studies.

2.6. Article identification procedure

Appropriateness was evaluated independently by two reviewers, PB and RL. To increase the number of papers available for full-text analysis, a second manual search was conducted. After evaluating English-language articles that

met the inclusion criteria, duplicates and non-qualifying items were noted and their exclusions explained. The reviewers separately evaluated the article data using a specific electronic form organized into the following categories: authors, year of study, aim of the study, materials and methods, and results.

3. Results

Overall, the included studies consistently reported an altered gut microbial profile in PD compared to controls, with recurrent differences involving taxa linked to SCFA production and intestinal inflammation. While the direction and magnitude of changes varied across cohorts and methodologies, several bacterial groups emerged repeatedly across studies, suggesting shared dysbiosis patterns that may relate to non-motor symptoms, disease severity, and metabolic readouts. The detailed findings are summarized below and then discussed study-by-study.

The databases Web of Science (269), PubMed (300), and Scopus (250) yielded a total of 819 publications. After de-duplication (n = 160), 659 unique records remained. Following an analysis of the abstracts and titles, 138 entries were removed. The remaining 521 papers were then obtained and validated. This method resulted in the elimination of 511 articles that were deemed off-subject. This study includes the qualitative analysis of the 10 final articles (Figure 1). The results of each investigation are shown in Table 1.

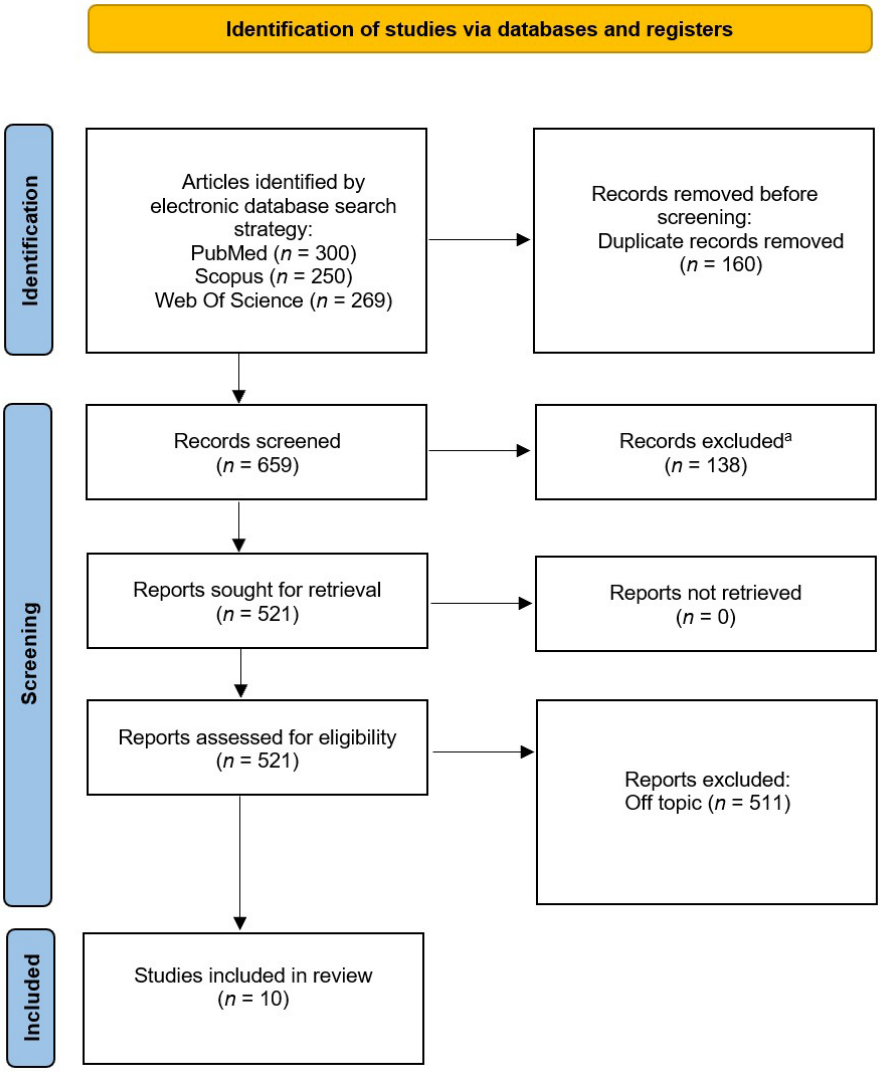

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of the literature search and article inclusion process.
Note: [a]Records excluded after title and abstract screening.

Table 1. Characteristics of included studies

Authors	Year	Study type	Aim	Methods	Results
Lin *et al.*[166]	2019	Cross-sectional	Evaluate gut microbiota alterations and inflammatory cytokine responses in PD patients	16S rRNA V3–V4 sequencing of 80 PD vs. 77 controls; plasma cytokines measured; independent validation cohort of 240 subjects (120 PD patients vs. 120 controls)	PD showed increased Verrucomicrobia, *Mucispirillum*, *Porphyromonas*, *Lactobacillus*, *Parabacteroides*; controls had higher *Prevotella*; Bacteroides correlated with UPDRS III and cytokines TNF-α and IFN-γ
Zhang *et al.*[5]	2020	Case-control	Compare gut microbiota of PD patients, healthy spouses, and unrelated controls	16S rRNA sequencing of 63 PD, 63 spouses, 74 controls; clinical phenotyping	Distinct microbiota among groups; inflammation-related taxa increased with Hoehn and Yahr stage. Seven taxa accurately discriminated PD (AUC 0.856)
Chen *et al.*[10]	2022	Observational	Assess relationships between SCFAs, gut microbiota, and PD severity	Fecal + plasma SCFAs quantified via mass spectrometry; metagenomic sequencing of microbiome; MDS-UPDRS & MMSEassessments	PD had ↓ fecal SCFAs but ↑ plasma SCFAs. Reduced fecal SCFAs correlated with motor severity; SCFA-producing bacteria lost their correlation with SCFA levels in PD
Lin *et al.*[167]	2025	Cross-sectional	Evaluate gut microbiota differences in PD patients with and without ICDs	16S rRNA sequencing of 191 PD patients (14 ICD+ vs. 177 ICD–)	No diversity differences; ICD patients enriched in *Methanobrevibacter* and *Intestinimonas butyriciproducens*; functional pathways related to xenobiotic degradation were elevated
Pietrucci *et al.*[168]	2020	Machine-learning study	Identify microbial signatures predictive of PD	Analysis of 846 metagenomic samples; ML algorithms (random forest, neural networks, SVMs)	Random forest best predicted PD status; 22 bacterial families identified as key discriminators
Lee *et al.*[169]	2025	Prospective observational (protocol)	Analyze effects of acupuncture/moxibustion on gut microbiome and PD symptoms	Analysis of 60 PD patients + 20 controls; 12-week acupuncture/ moxibustion; repeated microbiome sequencing and clinical assessments	Study ongoing; aims to correlate microbiome modulation with motor and non-motor symptom changes
Mao *et al.*[170]	2021	Cross- sectional	Describe microbiome alterations in PD patients in Central China	Shotgun metagenomic sequencing of 39 PD patients vs. 39 healthy spouses	PD showed enrichment in *Bilophila wadsworthia*, *Klebsiella*, and *Parasutterella* correlated with disease severity; *Prevotella* negatively correlated; functional pathways related to BCAA metabolism altered
Kwon *et al.*[171]	2024	Observational	Examine associations between diet and gut microbiota in PD patients	Analysis of 85 PD patients; 16S sequencing; dietary quality assessed via HEI-2015	Higher fiber led to ↑ butyrate-producers (*Butyricicoccus, Coprococcus*). High sugar led to ↑ *Klebsiella* and pro-inflammatory taxa. Healthy diet associated with reduced LPS-related genes

(*cont'd...*)

Table 1. (*Continued*)

Authors	Year	Study type	Aim	Methods	Results
Zapała *et al.*[172]	2021	Cohort study	Compare the microbiota of PD patients and healthy controls	Analysis of 27 PD patients on levodopa vs. 44 matched controls; NGS	PD had ↑ Bacteroides, Corynebacteria, Deltaproteobacteria, *Butyricimonas*, *Flavonifractor*, *Akkermansia muciniphila*, and *Eubacterium biforme*
Becker *et al.*[58]	2022	Interventional clinical trial	Assess effects of resistant starch on gut microbiota and symptoms	Analysis of 8-week RS intervention in PD; metagenomics; fecal SCFA and calprotectin measured	↑ fecal butyrate and ↓ calprotectin in PD + RS group; improved non-motor symptoms; stable α- and β- diversity across groups

Notes: ↑ Increased; ↓ Decreased.
Abbreviations: AUC: Area under the curve; BCAA: Branched-chain amino acid; HEI: Healthy eating index; ICDs: Impulse control disorders; IFN: Interferon; LPS: Lipopolysaccharide; PD: Parkinson's disease; RS: Resistant starch; SCFA: Short-chain fatty acid; SVMs: Support vector machines; TNF: Tumor necrosis factor; NGS: Next-generation sequencing; UPDRS III: Unified Parkinson's Disease Rating Scale, Part III.

3.1. Quality assessment

Overall, the included studies showed a predominantly low-to-moderate risk of bias across the Risk of Bias in Non-randomized Studies of Intervention (ROBINS-I) domains, with several concerns mainly related to confounding and participant selection (Table 2).

The quality of the papers included was evaluated by two reviewers, PB and RL, using the ROBINS-I approach. In non-randomized studies evaluating the health effects of two or more medications, ROBINS-I was created to assess the risk of bias. A bias degree was assigned to each of the seven criteria that were examined. In the event of a disagreement, the third reviewer, FI, was consulted until a resolution was reached. Any disagreements or disputes among reviewers were resolved through dialogue and consensus-building to improve the objectivity and consistency of the evaluations. A third reviewer made the final decision in cases of disagreement. Identifying the advantages and disadvantages of the evidence base helped provide a more accurate evaluation of the results' quality and dependability. By accounting for the likelihood of bias, we were able to draw informed interpretations and conclusions based on the evidence presented.

4. Discussion

4.1. General overview of microbiota alterations in patients with Parkinson's disease

The 10 studies selected for this review provide a robust, multidimensional understanding of gut microbiota alterations in PD, confirming dysbiosis as a recurrent, clinically meaningful signature across PD cohorts.[167-168]

Unlike earlier frameworks that relied on non-validated datasets, this discussion integrates only peer-reviewed articles using standardized sequencing or metabolomic approaches, ensuring methodological consistency and reliable interpretation.[167-169] Collectively, these studies demonstrate that dysbiosis is not an incidental by-product of PD but a component tightly associated with disease phenotype and systemic inflammatory responses.[170-171] Across the included literature, a reduction of SCFA-producing genera, particularly Faecalibacterium, Roseburia, and Butyricicoccus, is consistently reported, accompanied by an increase in inflammation-associated microbes, such as Enterobacteriaceae and Akkermansia.[172]

These compositional shifts are likely to contribute to impaired intestinal barrier integrity, increased endotoxin translocation, and chronic low-grade systemic inflammation, all of which are known to influence neurodegenerative pathways relevant to PD.[173-182]

Mechanistically, several gut–brain axis routes may plausibly link dysbiosis to neurodegenerative processes in PD. Reduced SCFA availability (particularly butyrate) may weaken epithelial integrity and immune tolerance, thereby increasing intestinal permeability and facilitating luminal endotoxin exposure. In parallel, expansion of pro-inflammatory taxa may enhance lipopolysaccharide-driven immune activation, promoting peripheral cytokine signaling and sustained low-grade systemic inflammation. These systemic signals may contribute to microglial priming and neuroinflammatory cascades, which are recognized contributors to neurodegenerative

Table 2. Summary of the main findings of the included studies investigating gut dysbiosis in patients with Parkinson's disease

Authors	D1	D2	D3	D4	D5	D6	D7	Overall
Lin *et al.*[166]	-	+	-	+	+	-	+	-
Zhang *et al.*[5]	+	+	-	+	+	+	+	+
Chen *et al.*[10]	-	+	-	+	+	-	+	-
Lin *et al.*[167]	-	+	X	-	+	+	-	-
Pietrucci *et al.*[168]	-	+	-	+	+	+	-	-
Lee *et al.*[169]	-	-	X	+	+	-	-	-
Mao *et al.*[170]	-	+	-	+	-	+	+	-
Kwon *et al.*[171]	-	-	-	+	+	-	+	-
Zapała *et al.*[172]	+	+	-	+	+	+	+	+
Becker *et al.*[58]	-	-	X	X	+	-	-	X

Notes: ! very high; X high; - some concerns; + low; ? no information; D1: Bias due to confounding; D2: Bias arising from the measurement of the exposure; D3: Bias in the selection of participants in the study (or into the analysis); D4: Bias due to post-exposure interventions; D5: Bias due to missing data; D6: Bias arising from the measurement of the outcome; D7: Bias in selection of the reported result.

vulnerability. Although most available clinical studies are observational and do not establish causality, these convergent mechanisms provide a biologically plausible framework through which gut microbial alterations could interact with α-synuclein-related pathology and disease progression, warranting confirmation in longitudinal and interventional cohorts.[183-190]

Taken together, these recurrent dysbiosis patterns support the evaluation of gut microbiota profiles as adjunct biomarkers for earlier identification and patient stratification in PD, pending validation in standardized longitudinal cohorts.

4.2. Microbial composition signatures and cross-population consistency

To support cross-population comparisons more transparently, Table 3 summarizes cohort geography (country/region), available contextual and dietary information, reported ethnicity, and the main taxa increased or decreased across the included PD studies. When such information was not reported in the original articles, this is

Table 3. Context of cross-population cohorts and main microbiome findings from the included Parkinson's disease studies

Study	Country/ region	Sample size (PD/controls)	Ethnicity	Diet/context	Method	Main taxa ↑ in PD	Main taxa ↓ in PD	Key clinical/ biomarker links
Lin *et al.*[166]	NR	80/77 (another validation cohort: 120/120)	NR	NR	16S rRNA V3-V4; plasma cytokines	Verrucomicrobia, *Mucispirillum*, *Porphyromonas*, *Lactobacillus*, and *Parabacteroides*	*Prevotella*	Bacteroides correlated with UPDRS III, TNF-α, and IFN-γ
Zhang *et al.*[5]	NR	63/74 (+63 spouses)	NR	Shared household environment	16S rRNA sequencing	Inflammation-related taxa ↑ with H&Y stage	NR	A total of 7 taxa discriminated PD (AUC 0.856)
Pietru cci *et al.*[168]	NR	846 samples	NR	NR	Metagenomics + ML (RF, NN, SVM)	22 bacterial families (not listed)	NR	RF best classifier of PD status
Mao *et al.*[170]	Central China	39/39 (spouses)	NR	Shared environment (spouses)	Shotgun metagenomics	*Bilophila wadsworthia*, *Klebsiella*, and *Parasutterella*	Prevotella	Severity correlated; altered BCAA pathways
Zapała *et al.*[172]	NR	27/44	NR	Levodopa users	NGS sequencing	*Bacteroides*, Corynebacteria, Deltaproteobacteria, *Butyricimonas*, *Flavonifractor*, *Akkermansia muciniphila*, and *Eubacterium biforme*	NR	NR
Chen *et al.*[10]	NR	NR	NR	NR	SCFAs (MS); metagenomics; UPDRS, MMSE	NR	NR	↓ fecal SCFAs ↑ plasma SCFAs; motor severity correlation
Becker *et al.*[58]	NR	NR	NR	Resistant starch (8 weeks)	Metagenomics; SCFAs; calprotectin	NR	NR	↑ butyrate, ↓ calprotectin; improved non-motor symptoms
Kwon *et al.*[171]	NR	85/NR	NR	Diet quality (HEI- 2015)	16S rRNA sequencing	*Butyricicoccus* and *Coprococcus* (induced by high fiber)	NR	High sugar ↑ *Klebsiella*; LPS-related genes ↓ with a healthy diet
Lin *et al.*[167]	NR	191/177 (ICD^+ vs. ICD^-)	NR	NR	16S rRNA sequencing	*Methanobrevibacter* and *Intestinimonas*; produced butyric acid	NR	Xenobiotic degradation pathways ↑
Lee *et al.*[169]	NR	60/20	NR	Acupuncture/moxibustion	Repeated microbiome sequencing	NR	NR	Study ongoing

Notes: ↑ Increased; ↓ Decreased; Dietary habits and ethnicity were inconsistently reported across the included studies.

Abbreviations: AUC: Area under the curve; BCAA: Branched-chain amino acid; H&Y stage: Hoehn and Yahr stage; HEI: Healthy eating index; ICDs: Impulse control disorders; IFN: Interferon; LPS: Lipopolysaccharide; MMSE: Mini-mental state examination; ML: Machine learning; MS: Mass spectrometry; NN: Neural network; NR: Not reported; PD: Parkinson's disease; RF: Random forest; RS: Resistant starch; SCFA: Short-chain fatty acid; SVMs: Support vector machines; TNF: Tumor necrosis factor; NGS: Next-generation sequencing; UPDRS: Unified Parkinson's Disease Rating Scale.

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indicated as not reported. For instance, Lin *et al.*[166] reported increased abundance of *Lactobacillus*, *Parabacteroides*, and Verrucomicrobia, together with reduced *Prevotella*, a pattern replicated in multiple independent cohorts, although the magnitude and direction of some taxa varied across populations and analytical pipelines.

Importantly, these compositional changes were associated with systemic immune alterations, including elevated levels of tumor necrosis factor-α and interferon-γ, linking gut dysbiosis to inflammatory pathways implicated in PD pathophysiology.[191-193] Similarly, Zapała *et al.*[172] and Mao *et al.*[170] identified increased abundance of *Akkermansia muciniphila* and *Bilophila wadsworthia*, taxa involved in mucin degradation and bile resistance.

Together, these findings reinforce the concept of a shared "pro-inflammatory enterotype" in PD, largely independent of geographic or environmental background. Cross-population consistency of key microbial signals strengthens their translational potential and supports future use in risk stratification and prognostic modeling, provided findings are externally validated using harmonized sampling and analytical pipelines.

4.3. Functional and metabolomic alterations

Functional alterations of the microbiome, particularly in SCFA metabolism, have emerged as central features of dysbiosis in PD.[194-203] Chen *et al.*[10] reported reduced fecal SCFA concentrations in PD patients, especially butyrate, despite increased circulating levels, suggesting impaired mucosal uptake and epithelial dysfunction.

Lower fecal SCFA concentrations are correlated with more severe motor impairment and poorer cognitive scores, supporting a mechanistic link between microbial metabolites and neural function.[204] The interventional RESISTA-PD trial conducted by Becker *et al.*[58] further demonstrated that resistant starch supplementation increases fecal butyrate, reduces intestinal inflammation, and improves gastrointestinal and non-motor symptoms in PD. This highlights the therapeutic potential of restoring SCFA-producing bacterial communities.[205] Environmental influences, including diet, also play a major role in determining microbiota composition in PD. Zhang *et al.*[5] showed that even when PD patients live with healthy spouses, their microbiota profiles remain significantly distinct, indicating that dysbiosis is not solely driven by shared dietary or environmental factors.

Kwon *et al.*[171] found that higher fiber consumption is associated with greater abundance of beneficial butyrate-producing taxa, while high sugar consumption promotes proliferation of Klebsiella and other pro- inflammatory organisms.

This suggests that dietary interventions could complement pharmacological therapy by creating a gut environment less conducive to inflammatory and neurodegenerative processes. Convergent functional and metabolomic findings provide a strong rationale for microbiota- targeted dietary and metabolic interventions as adjunctive strategies in PD management.

More broadly, human studies indicate that microbiome-targeted interventions can be clinically actionable in selected conditions, providing a translational precedent for microbiota-based therapies.[58,169-172] In PD, however, interventional evidence remains limited and heterogeneous, and adequately powered trials with harmonized clinical and microbiome endpoints are required before routine clinical adoption.

4.4. Gut dysbiosis and non-motor symptoms in Parkinson's disease

Non-motor features—such as cognitive deficits, mood symptoms, and autonomic dysfunction—show meaningful associations with dysbiosis.[173-182] Lin *et al.*[167] described distinct microbiome patterns among PD patients with impulse-control disorders, particularly increased *Methanobrevibacter* and *Intestinimonas butyriciproducens*.

Other studies identified links between microbial alterations and gastrointestinal dysfunction, anxiety, sleep disturbances, and cognitive decline, suggesting that gut microbes influence both the central and enteric nervous systems.[183-190] These associations reinforce the concept that gut microbiota act across a wide clinical spectrum in PD, extending beyond motor impairment.[191-192]

Machine-learning approaches illustrate the diagnostic potential of microbial biomarkers.[193-197] Pietrucci *et al.*[168] demonstrated that microbial signatures can classify PD with high accuracy using random forests, support vector machines, and neural networks.

At present, microbiome-based diagnostics for PD remain investigational and are unavailable as approved clinical tests. Despite advances in metagenomics and bioinformatic approaches, translation into clinical diagnostics is limited by substantial inter-cohort heterogeneity (diet, medication use, constipation severity, and geography), methodological variability in sampling and sequencing, batch effects, and insufficient external validation across independent populations.

While preliminary, these data suggest that microbiome-based diagnostic tools may complement current clinical scales and eventually contribute to early detection.[195-204] Future work should aim to standardize microbial classifiers to ensure reproducibility across studies and cohorts.

Microbiota profiles may support symptom-based phenotyping and contribute to future diagnostic and prognostic frameworks, particularly for non-motor manifestations of PD.

4.5. Limitations, future directions, and clinical implications

Despite promising findings, several limitations are consistently noted across studies. Sample sizes are often modest, reducing statistical power and hindering detection of smaller but clinically meaningful effects. Heterogeneity in sequencing methods (16S vs. shotgun), data processing pipelines, and confounding factors, such as medication use, constipation severity, and dietary intake, limits comparability across studies. Longitudinal studies remain scarce, hindering our ability to determine causality or assess whether dysbiosis precedes PD onset.

Future research should prioritize large, multi-center, longitudinal cohorts with harmonized methodologies, dietary control, and integrated host biomarker profiling. Gut-focused interventions, including prebiotics, probiotics, resistant starch, and microbiota-centered non-pharmacological interventions, represent promising avenues for modifying disease progression. Ultimately, a more nuanced understanding of gut–brain interactions may enable personalized therapeutic approaches for PD based on individual microbial signatures.

Although the microbiome–PD literature has expanded over the last decade, only a limited number of studies met our predefined eligibility criteria, which prioritized human cohorts, original peer-reviewed data, standardized microbiome/metabolomic methodologies, and sufficient reporting for extraction and comparison. Numerous publications were excluded because they were narrative reviews, preclinical studies, conference abstracts, or lacked extractable and methodologically comparable microbiome outcomes. This limited yield underscores the need for harmonized protocols, adequate sample sizes, and longitudinal designs to improve reproducibility and clinical translation; nevertheless, synthesizing the best available standardized evidence remains valuable to delineate the most recurrent signals and to guide future study design.

5. Conclusion

This systematic review underscores an expanding body of literature linking changes in the gut microbiota to the clinical expression and progression of PD. Across the 10 selected studies, consistent dysbiotic patterns emerged, particularly lower abundance of SCFA-producing bacteria and higher levels of taxa linked to inflammation and mucosal barrier disruption. Importantly, several studies demonstrated meaningful associations between microbial imbalances and both motor and non-motor manifestations, including gastrointestinal impairment, autonomic impairment, and behavioral disturbances, suggesting a broad impact of gut dysbiosis on the clinical phenotype of PD.

The inclusion of interventional studies provided further insight into the potential therapeutic relevance of the gut microbiota. Approaches such as resistant starch supplementation and acupuncture demonstrated the capacity to modulate microbial composition and improve select clinical outcomes, while machine-learning analyses offered promising evidence for the development of microbiome-driven diagnostic tools. Collectively, these findings highlight the gut–brain axis as a promising frontier for mechanistic insight and therapeutic innovation in PD.

Nevertheless, the limitations identified across the selected studies emphasize the need for more rigorous and standardized research. Large-scale, longitudinal studies with harmonized microbiota sequencing methods, comprehensive assessment of confounders, and integration of host biological markers will be critical for determining whether microbiota alterations are causal contributors to PD or secondary phenomena. As the field progresses, microbiota-centered diagnostics and targeted interventions may ultimately support more personalized and effective management strategies for individuals with PD. By synthesizing the most consistent microbiota and metabolomic alterations in PD, this review provides clinicians and researchers with a concise evidence base to support patient stratification hypotheses and to guide the design of standardized, longitudinal, and interventional studies.

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