Five-Year Follow-Up of Photobiomodulation in Parkinson's Disease: A Case Series Exploring Clinical Stability and Microbiome Modulation

Abstract

Background: Parkinson's disease (PD) involves progressive neurodegeneration with clinical or subclinical disturbance of the gut–brain axis, including altered gastrointestinal motility and enteric nervous system involvement. Clinical studies have reported gut microbiome alterations in PD, with shifts in taxa associated with inflammatory signalling and short-chain fatty acid (SCFA) metabolism. Photobiomodulation (PBM), a non-invasive light therapy, has been investigated as a potential adjunctive treatment for PD, with proposed effects on neural, metabolic, and immune pathways. We previously reported the five-year clinical outcomes in a PBM-treated Parkinson's disease case series. Here we report the five-year gut microbiome outcomes based on longitudinal samples collected from the same participants. This was an exploratory, open-label longitudinal study without a control group. **Objective**: Our objective was to assess whether long-term PBM was associated with changes in gut microbiome diversity and composition in the same Parkinson's disease cohort as previously assessed for changes in Parkinson's symptoms. **Methods**: Six participants from the earlier PBM proof-of-concept study who had been diagnosed with idiopathic PD and who had continued treatment (transcranial light emitting diode [LED] plus abdominal and neck laser) for five years had their faecal samples analysed by 16S rDNA sequencing to assess microbiome diversity and taxonomic composition. **Results**: Microbiome analysis revealed significantly reduced evenness (α-diversity) and significant shifts in β-diversity over five years, as assessed by Permutational Multivariate Analysis of Variance (PERMANOVA). At the phylum level, Pseudomonadota and Methanobacteriota decreased in four of the six participants. Both of these phyla are often increased in the Parkinson's microbiome compared with the microbiomes of healthy controls. Family-level changes included increased acetate-producing Bifidobacteriaceae (five of the six participants); decreased pro-inflammatory, lipopolysaccharide (LPS)-producing Enterobacteriaceae (two of the three participants who have this bacterial family present); and decreased LPS- and H_2S-producing Desulfovibrionaceae (five of six). At the genus level, *Faecalibacterium*, a key butyrate producer, increased in four of the six participants, potentially leading to more SCFA availability, although other SCFA-producing bacteria were decreased. This was accompanied by reductions in pro-inflammatory LPS and H_2S-producing genera that are often increased in the Parkinson's microbiome. **Conclusions**: This five-year case series represents the longest follow-up of microbiome changes in Parkinson's disease, although the interpretation of results is limited by very small numbers, the lack of a control group, and the inability to control for lifestyle influences such as dietary changes. While causal relationships cannot be inferred, the parallel changes in improvements in mobility and non-motor Parkinson's symptoms observed in this cohort, raises the hypothesis that PBM may interact with the gut–brain axis via the microbiome. Controlled studies incorporating functional multi-omics are needed to clarify potential mechanistic links between microbial function, host metabolism, and clinical outcomes.

Keywords: Parkinson's disease, microbiome, photobiomodulation, short-chain fatty acids, lipopolysaccharide, hydrogen sulphide

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterised by α-synuclein aggregation, dopaminergic neuronal loss in the substantia nigra, and attendant motor and non-motor symptoms [1]. It is increasingly recognised as a multisystem disorder, involving both central neurological changes and peripheral disturbances of the gut–brain axis. It has recently been hypothesised that the heterogeneous nature of Parkinson's symptoms might be explained by PD being acquired as brain-first (central nervous system [CNS]) or body-first (peripheral), depending on the origin of the α-synuclein pathology [2]. There is ample evidence from animal models that α-synuclein aggregation can originate in the enteric nervous system and then spread to the CNS [3,4]. Converging evidence has highlighted the role of gut–brain axis dysfunction in PD pathophysiology [5,6,7], with dysbiosis in the gut microbiome being a common feature of idiopathic PD [8,9,10,11] with

microbiome differences in the body-first and brain-first subtypes [12]. Gastrointestinal symptoms, including microbiome disruption characterised by loss of short-chain fatty acid (SCFA) producing taxa and increases in pro-inflammatory bacteria, often precede motor manifestations by years, suggesting early involvement of the gut and its microbiome [13]. Microbiome changes have been linked to impaired intestinal integrity, heightened inflammation, and increased neural vulnerability [10,14,15], as well as PD progression [9,16,17,18].

Current microbiome-targeted interventions for PD, including dietary modification, prebiotics, probiotics, and faecal microbiota transplantation (FMT), show promise but with inconsistent clinical benefits, highlighting the need for novel approaches to modulate the microbiome-gut–brain axis.

Photobiomodulation (PBM) is a non-invasive therapy using non-thermal red to near-infrared light [19,20], and has shown neuroprotective and immunomodulatory effects in preclinical PD models [21,22], with emerging evidence from clinical trials [23,24,25,26]. Early reports also indicate that PBM might modulate the gut microbiome in animal models [27] and in small human studies [28,29], including increases in beneficial SCFA producers and reductions in pro-inflammatory bacteria. We have previously described sustained clinical stability in a small cohort of study participants who have used long-term PBM therapy [24]. The present study builds directly on these clinical observations by examining the corresponding five-year gut microbiome profiles in the same participants, providing an exploratory insight into the effect of prolonged PBM on longitudinal changes in the microbial composition of the gut while acknowledging that other factors, such as dietary changes, aging, and medications, may also influence microbiome changes.

2. Methods

2.1. Study Design and Participants

This was an open-label, longitudinal follow-up study of participants from a previously reported PBM proof-of-concept study of PD [24,26]. Six participants from an original proof-of-concept study, with clinically diagnosed idiopathic PD, continued PBM treatment for five years (Table 1). The remaining six participants from the original study had either been diagnosed with an alternative disease (multisystem atrophy, two participants) or had discontinued PBM treatment due to their partner passing away and relocation to an aged care facility (one participant); recovery from cancer therapy (one participant); or declining to continue PBM treatment (two participants). All continuing participants had participated in earlier PBM studies conducted under approved clinical research protocols and provided renewed informed consent. All indicated that they had continued PBM therapy with varying degrees of consistency for five years [24].

Table 1.

Demographic characteristics of participants.

		Participants					
		A2	A5	B1	B2	B4	B5
Sex		F	M	F	F	M	F
Age	Baseline	79	72	58	77	75	67
	5 years	84	77	63	82	80	72
s since diagnosis at baseline		1	not reported	3	7	2	7
ehn and r stage	Baseline	2	2	2	3	1	2
	5 years	3	2	2	3	2	2
Affected side		L	L	L	L	L	R
Medications		Madopar bd HBS nocte	Sinemet 7 × d Sifrol mane	Kinson 7 × d	Kinson QID	Madopar bd	Stalevo QID
Daily L-dopa		600 mg	700 mg	170 mg	400 mg	600 mg	800 mg
MDS-DRS-III	Baseline	20	15	23	54	18	20

CORE	5 years	24	15	21	23	12	19
alls in 5 years		0	0	0	0	0	0
ange in sense of smell		Improvement from hyposmia	Unchanged	Slow improvement	Substantial improvement from >5 years of anosmia	Improvement from anosmia	Slowly deteriorating
r dietary changes over 5 yrs		No	No	? less healthy after year 2	No	No	Reduced carbohydrates 2 years into study
Exercise		Bike 20 min/day	Unanswered	Bike 30–40 km/week	Gardening + incidental (stairs)	Walking 5–6000 steps/day	PD-specific exercises 1× per week
Helmet used		SYMBYX	VIELIGHT	SYMBYX	WELL RED	VIELIGHT	SYMBYX

Open in a new tab

F = female; M = male; L = left side; R = right side; bd = twice daily; QID = 4 times daily; nocte = at night; 7 × d = 7 times per day; mane = in the morning; ? = possibly.

2.2. Intervention

Participants self-administered at-home PBM three times weekly using a combination of transcranial, cervical, and abdominal irradiation, as previously described [26]. The abdomen and neck were irradiated using a near-infrared 904 nm Class 1 laser and one of three light emitting diode (LED) devices on the head (Supplementary Table S1). Treatment protocols were based on previously published PBM parameters shown to modulate motor and cognitive outcomes in PD and were maintained with minimal adjustment throughout the five-year period. There were a number of confounding factors that could have contributed to microbiome changes over time, such as dietary changes, aging, medications, and changes in exercise patterns. These were not directly monitored but self-reported by participants at the 5-year assessment.

2.3. Sample Collection, DNA Extraction, and 16S rRNA Gene Sequencing

Stool samples were collected from each participant at baseline and after five years of continuous PBM. Samples were immediately frozen at −80 °C until analysis. Total bacterial DNA was extracted using the Qiagen PowerSoil DNA Isolation Kit following the manufacturer's instructions, with modifications to optimise yield from low-biomass samples. DNA quality and concentration were verified by NanoDrop spectrophotometry and agarose gel electrophoresis.

All sequencing and bioinformatics analyses were performed with participant identity masked. 16S rRNA gene sequencing was chosen to maintain methodological consistency with prior analyses and as a cost-effective method for community-level profiling. The V3–V4 regions of the bacterial 16S rRNA gene were amplified using universal primers and sequenced on an Illumina (San Diego, CA, USA) MiSeq platform (2 × 300 bp paired-end reads) in two separate sequencing runs (baseline and 5 years). Raw reads were quality-filtered, denoised, and clustered into amplicon sequence variants (ASVs) using the QIIME 2 pipeline (v2024.4) with DADA2 [30]. All samples were retained after denoising. The total number of sequencing reads was 933,105, with a mean sequencing depth of 70,758. Sampling depth (33,000) was set to the shallowest sample (A2 baseline), ensuring that Shannon alpha-rarefaction had plateaued for all samples. Negative extraction and sequencing controls were included, and sequence quality metrics were assessed prior to analysis. No contaminant signatures were identified in the controls or samples; thus, decontamination tools were not applied. Taxonomy was assigned against the Greengenes2 database [31]. Alpha (α-) diversity metrics (Observed Features, Shannon index, Faith's Phylogenetic Diversity, and Pielou Evenness Index) were computed with QIIME 2 using the Kruskal–Wallis Test. Beta (β-) diversity was assessed using permutational multivariate analysis of variance (PERMANOVA), with 999 iterations for unweighted and weighted UniFrac distances visualised by principal coordinate analysis using the EMPeror plugin [32]. Changes in genus abundance between groups were tested with the Analysis of Compositions of Microbiomes (ANCOM) plugin [33] after centred log-ratio transformation. Relative abundance was determined at the phylum, family, and genus levels. At the phylum level, the various Bacillota phyla were combined to allow comparison with earlier studies. Taxa changes were exploratory, using a 2-fold difference in relative abundance as the threshold for change. Taxonomic changes were interpreted with reference to published

PD microbiome signatures [9,10,11,16,34,35,36,37,38,39,40,41,42,43,44,45], with particular attention to taxa associated with SCFA production and with inflammatory potential.

2.4. Ethical Approval

All procedures complied with the Declaration of Helsinki and were approved by the Griffith University Human Research Ethics Committee (approval code 2018/16, approved 3 February 2018) with an extension until 24 April 2024. This study was registered with the Australian New Zealand Clinical Trials Registry (ANZCTR—a primary registry in the WHO International Clinical Trial Registry Platform), registration number ACTRN12618000038291p, registered on 12 January 2018. Written informed consent was obtained from all participants.

3. Results

Participants did not report any adverse events due to the PBM treatment. The participants reported that they had no major dietary changes during the 5-year PBM intervention, although one indicated that their diet may have been "less healthy" compared with the first year and one that they had reduced their carbohydrate intake at 2 years in order to lose weight (Table 1). The participants had been diagnosed with PD between 2 and 7 years before beginning this study in 2019, and five of the six participants showed no decline in Movement Disorder Society Unified Parkinson's disease Rating Scale (MDS-UPDRS-III [motor examination]) scores over the 5-year intervention period (Table 1). All participants were using dopamine replacement therapy.

3.1. Microbiome Diversity

There was no significant change in the α-diversity measures of richness as determined by the Observed Features measure or Faith's Phylogenetic Diversity. However, Pielou's Evenness Index was significantly reduced (Kruskal–Wallis test, $q = 0.016$), as was the Shannon Index (Kruskal–Wallis test, $q = 0.025$) (Figure 1A). There was also a significant shift in β-diversity between baseline and 5 years for both unweighted and weighted UniFrac metrics (PERMANOVA, $q = 0.003$ and $q = 0.036$, respectively) (Figure 1B).

Figure 1.

Open in a new tab

Diversity analysis of gut microbiome samples before PBM treatment (baseline) and after 5 years of PBM treatment. (**A**) The α-diversity showing no significant differences in richness indices (Observed Features and Faith's PD), but significant differences in the Pielou's Evenness Index (Kruskal–Wallis test, q = 0.016) and the Shannon index (Kruskal–Wallis test, q = 0.025). (**B**) The β-diversity, showing significant differences between baseline and 5 years for unweighted UniFrac (PERMANOVA, q = 0.003) and weighted UniFrac (PERMANOVA, q = 0.036), as well as PCoA plots. Blue = baseline; Orange = 5 years.

3.2. Taxonomic Changes

Changes in microbiome composition at the phylum, family, and genus taxonomic levels are shown in Supplementary Table S2. Taxonomic changes and their functional interpretations are summarised in Table 2.

Table 2.

Phylum-, family-, and genus-level microbiome changes after 5 years of PBM in a small PD cohort (n = 6). Taxa changes are presented primarily as exploratory, using a 2-fold difference in relative abundance as the threshold for change. Statistical inference using ANCOM identified a significant increase in *Collinsella*.

Taxa	Functional Relevance	Change in PD vs. HCs	Change over 5 Years				Mean % in Microbiome
			Incr.	Decr.	nc	nd	
Phylum							
Bacillota	Contains many SCFA producers	Often depleted [8,10]	2	4	-		17.055
Actinomycetota	Mixed functions, some beneficial		6	0	-		17.550
Bacteroidota	Contains SCFA producers as well as pathobionts	Can be enriched [8,46] or depleted [47]	2	4	-		9.832
Pseudomonadota	Contains many pathobionts	Enriched in PD [48]	2	4	-		0.762
Desulfobacterota	H_2S-producing bacteria	Enriched in PD [49]	1	5	-		0.206
Methanobacteriota	CH_4-producing	Enriched in PD [9]	2	4	-		0.862
Family							
Ruminococcaceae	Contains SCFA producers	Can be depleted [50] or enriched [11]	3	3	-		7.500
Bifidobacteriaceae	Contains SCFA producers, anti-inflammatory, contains probiotic species	Often enriched [38,51]	5	1	-		12.501
Enterobacteriaceae	Gram-negative, LPS producers, implicated in neuroinflammation	Often enriched [10]	1	2	-	3	0.123
Desulfovibrionaceae	H_2S producers	Enriched [52], linked to α-synuclein aggregation [52]	0	5	1	-	0.205
Erysipelotrichaceae	Contains SCFA producers, increased in inflammatory diseases [53] and disrupted lipid metabolism [54]	Enriched [38] or depleted [55], correlated with worsening UPDRS-III [38]	1	5	-		0.868
Genus							
SCFA Producers Reported as Reduced in PD Compared to HCs							
Faecalibacterium	Key SCFA producer, anti-inflammatory, supports gut barrier, reduces systemic and neuroinflammation	Depleted in PD [56,57,58]	4	1	1	-	3.019
Anaerostipes	SCFA producer	Depleted [9], protective against PD [59]	0	2	4	-	2.635
Blautia	SCFA producer	Reduced in PD [60], negatively associated with PD severity [61]	1	2	3	-	13.194
Roseburia_A	SCFA producers, anti-inflammatory, reduces systemic and neuroinflammation	Reduced in PD [60]	0	5	-	1	0.872
Roseburia_C			0	4	-	2	0.149
Agathobacter_187866	SCFA producers, anti-inflammatory	Reduced in PD [60]	1	2	2	1	0.275
Agathobacter_121497			0	4	0	2	0.265
SCFA Producers Reported as Increased in PD Compared to HCs							

Bifidobacterium	SCFA producer, enhances tight junctions [62], neuroprotective in other models	Often enriched [8], but low levels found correlated with faster progression [63]	4	0	2	-	12.498
Alistipes	SCFA producer, mixed roles, beneficial and detrimental (IBD) effects [64]	Often enriched [9]	2	4	-	-	1.169
Parabacteroides	SCFA producer, anti-inflammatory in the microbiome	Can be enriched [65]	1	4	1	-	1.486
SCFA Producers Reported as Either Reduced or Increased in PD Compared to HCs							
Gemmiger	SCFA producer	Sometimes enriched [66], other times depleted	1	3	2	-	3.533
Prevotella	Some strains related to dysbiosis, SCFA producer	Can be depleted [67] or enriched [68], inversely correlated with disease progression [34]	3	0	-	3	0.622
Turicibacter	SCFA producer, modifies bile acids, reduces cholesterol and triglycerides (mice)	Depleted [16] or enriched [69]	4	1		1	0.065
Eubacterium_R	SCFA producers, mixed species	Depleted [70] or enriched [71], some species correlated with higher UPDRS [70]	0	4	1	1	0.630
Eubacterium_J			1	3	-	2	0.364
Eubacterium_G			1	5	-	-	0.163
Eubacterium_F			1	1	1	3	0.083
Eubacterium_I			0	2	2	2	0.078
Butyricimonas	SCFA producers	Enriched in PD [71], higher abundance correlated with worse cognitive symptoms [72] but better non-motor symptoms in one study [45]	4	0	1	1	0.054
Ruminococcus_B	SCFA producers, strain-specific interactions in health and disease [73]	Can be depleted [69] or enriched in PD [42]	0	4	-	2	0.234
Ruminococcus_E			1	3	1	1	0.042
Bacteroides	SCFA producers, some pro-inflammatory strains	Enriched [74] or depleted [67] in PD, low levels correlated with faster progression [63]	2	4	-	-	5.051
Pathobionts—Reported as Enriched in PD Compared to HCs							
Streptococcus	Pathobiont	Enriched in PD [8]	1	0	5	-	2.381
Limiplasma	Unknown	Enriched in PD [9], correlated with PD severity [75]	2	2	1	1	0.375
Collinsella	Related to a high-protein and low-fibre diet [76], may be pro-inflammatory	Enriched in PD in some studies [36,66], depleted in one Indian study [37], related to Lewy Body dementia [77], correlated with faster PD progression [35]	5	1	-	-	3.905
Methanobrevibacter	Archean CH_4 producer	Enriched in PD [9]	0	2	1	3	0.190
Klebsiella	LPS producer	Enriched in PD [65]	1	2	-	3	0.110
Bilophila	H_2S producer	Correlated with PD progression [35]	1	3	-	2	0.059
Desulfovibrio	H_2S producer	Enriched, correlated with worsened MDS-UPDRS-III and IV [38]	0	2	2	2	0.139
Holdemania	Associated with obesity [78]	Over-represented in PD [42]	0	6	-	-	0.054

Other Genera							
Barnesiella	Mixed effects, may ameliorate T2D [79]	Reduced abundance correlated with faster PD progression [80]	3	3	-		0.402
Akkermansia	Mucin degrader, gut barrier support [81]	Often enriched [35], may induce α-synuclein in vitro [82], neuroprotective in a mouse model of PD [83]	2	4	-	-	2.234

Open in a new tab

PD = Parkinson's disease; HCs = healthy controls; SCFA = short-chain fatty acid; MDS-UPDRS = Movement Disorder Society Unified Parkinson's disease Rating Scale; nd = not detected; nc = no change.

Phylum-level changes (Figure 2A) in the eight most common phyla showed increases in Actinomycetota in all participants (six of six) and decreases in unclassified bacteria (five of six), Bacillota (four of six), Bacteroidota (four of six), and Pseudomonadota (four of six).

Figure 2.

Open in a new tab

Taxonomic changes in the gut microbiome from before PBM treatment (baseline) to after 5 years of PBM treatment at the phylum and family taxonomic levels. (**A**) Composition of phyla for each participant and mean composition before PBM treatment and after 5 years of treatment. (**B**) Composition of families for each participant and mean composition before PBM treatment and after 5 years of treatment. (**C**) Selected family changes from baseline to after 5 years of PBM treatment.

Family-level changes (Figure 2B) in the 45 most common families showed increases in Bifidobacteriaceae in five of the six participants and Ruminococcaceae in half of the participants (Figure 2C). Enterobacteriaceae, Erysipelotrichaceae, and Desulfovibrionaceae were mostly decreased in 5-year microbiomes (Figure 2C).

Genus-level changes for the 122 most common genera showed that SCFA-producing bacteria both increased and decreased over 5 years. *Faecalibacterium* was increased in four of the six participants in the current study (Figure 3B): in one participant (B4), increased to 13.6% of the microbiome. Other SCFA-producing bacteria, *Roseburia*_A_166204 and *Roseburia_C*, showed decreases in five of five and four of four participants, respectively, from low proportions (<1%) in most participants. *Anaerostipes* decreased in two of the six participants, with the remaining four showing no change. *Blautia_A_141781* was overall the most common genus, representing up to 32.2% of the microbiome. *Blautia* decreased in two participants with lower proportions of the genus in their microbiomes (6.07% and 0.80%). Other prominent SCFA producers that have been reported as depleted in PD microbiomes (such as *Butyrivibrio* and *Butyribacterium*) were either detected at very low levels (in one participant only) or not detected, suggesting that these may have been substantially reduced or eliminated during the years of dysbiosis. Other SCFA-producing genera have been reported as being increased in PD microbiomes (Table 2), such as *Bifidobacterium,* which increased in four of the six participants, while *Alistipes* and *Parabacteroides* decreased in the majority of participants (Figure 3C). SCFA-producing genera that have been reported as increased in PD in some studies and decreased in other studies (Table 2) also showed either increases in the majority of participants (*Butyricimonas, Prevotella, Turicibacter*) or decreases (*Bacteroides* and the various *Eubacterium* genera) (Figure 3D).

Figure 3.

Open in a new tab

Taxonomic changes in the gut microbiome from before PBM treatment (baseline) to after 5 years of PBM treatment at the genus level. (**A**) Composition of genera for each participant and mean composition before PBM treatment and after 5 years of treatment. (**B**) Selected genus changes from baseline to after 5 years of PBM for genera reported in the literature as SCFA-producing and depleted in the PD microbiome. (**C**) Selected genus changes from baseline to after 5 years of PBM for genera reported in the literature as SCFA-producing and enriched in the PD microbiome. (**D**) Selected genus changes from baseline to after 5 years of PBM for genera reported in the literature as SCFA-producing and either enriched or depleted in the PD microbiome. (**E**) Selected genus changes from baseline to after 5 years of PBM for genera reported in the literature as pathobionts and/or pro-inflammatory.

Many pathobionts and pro-inflammatory genera that were detected in the 122 most common genera showed a decline in the majority of participants (Figure 3E), including *Bilophila* (three of four), *Desulfovibrio* (two of four, with two unchanged), *Methanobrevibacter* (two of three), and *Klebsiella* (two of three), while *Limiplasma* increased in two and decreased in two participants. *Streptococcus* increased in one participant and was unchanged in the other five. In each of these cases, the genera were at low levels (<1%) at baseline, apart from two participants with higher proportions of *Streptococcus* (8.59% and 5.32%), both of whom showed a small (less than 2-fold) decrease over 5 years. *Collinsella* is another pathobiont that is increased in the PD microbiome. It was the only genus to show a significant change (increase) over the 5 years, as detected by the ANCOM statistic, and was increased in five of the six participants to between 4% and 18% of the microbiome. Another conspicuous pathobiont change was the increase in *Enterococcus_B* in one participant (A2) from non-detected at baseline to becoming the dominant genus at 5 years (45.5% of the total microbiota).

Genera considered to be generally healthy in other contexts but that are increased in the PD microbiome include *Akkermansia, Bifidobacterium*, and *Lactobacillus* (Table 2). *Akkermansia* decreased in four of the six participants in the current study (Figure 3E), although one participant showed an increase in *Akkermansia* to 18% of the microbiome. The proportion of *Lactobacillus* in the samples was below the threshold for inclusion in this analysis.

There are a number of genera that have been considered to be potential markers of PD progression (Table 2). Putative bacterial markers correlated with PD severity and more rapid PD progression include Desulfovibrionaceae, Erysipelotrichaceae, *Desulfovibrio*, *Bilophila*, *Limiplasma*, and *Eubacterium*, all of which, apart from *Limiplasma*, showed decreases over 5 years in the majority of participants. Putative bacterial markers inversely correlated with PD progression (*Bifidobacterium*, *Prevotella, Butyricimonas*) showed increases in the majority of participants, except for *Bacteroides*, which was decreased in the majority of participants.

4. Discussion

4.1. Longterm Clinical Stability

This study provides the longest reported follow-up of individuals with PD who have continued PBM therapy, extending the previous report of five-year clinical outcomes [24], to include parallel gut microbiome observations. In the earlier clinical analysis of this cohort, most participants who continued PBM therapy demonstrated sustained stability or improvement in mobility, balance, and non-motor features such as cognition and olfaction, with no serious adverse events reported. This stability or improvement in the MDS-UPDRS-III score can be contrasted with the expected decline of between 1.4 and 8.9 points annually in untreated or L-dopa-medicated PD patients [84].

Taken together with the changes in the microbiome, the findings suggest that long-term PBM was well-tolerated in this small cohort and was associated with sustained clinical stability alongside longitudinal changes in gut microbiome composition. While no causal inferences can be drawn, the co-occurrence of clinical stability and microbiome shifts provides a basis for further investigation in controlled studies.

4.2. Microbiome Shifts

Participants reported no major changes to their diets over the five years of this study, suggesting that large dietary changes were unlikely to account for the observed microbiome changes. Significant longitudinal changes were detected in both α- and β-diversity. The reduction in α-diversity evenness, reflected by lower Pielou's Evenness and Shannon indices, indicates increasing dominance of specific microbial taxa within the microbiome community over time. While cross-sectional studies of PD have not consistently reported differences in α-diversity compared to healthy controls (HCs), several studies have described a significant increase in the α-diversity in PD cohorts compared to HCs [35,69,85,86].

Significant changes in both unweighted and weighted UniFrac indices indicate global restructuring of the microbial community. Changes in unweighted UniFrac are consistent with shifts in the presence or absence of microbial lineages, whereas changes in weighted UniFrac suggest alterations in the relative proportions of taxa present. Significant differences in β-diversity are commonly reported in cross-sectional studies [9,56], and the present findings demonstrate that comparable compositional shifts can also occur longitudinally within individuals.

To further interpret diversity shifts, an exploratory assessment of changes in taxonomic composition was undertaken. At the phylum level, reductions were observed in the relative proportion of Pseudomonadota (formally Proteobacteria), a group frequently reported as increased in PD microbiomes and with many pathobiont and pro-inflammatory members [74]. A reduction in Methanobacteriota was also observed. This is a phylum of methane-producing archaea that are also reported as increased in PD microbiomes [9]. At the family level, the relative abundance of Bifidobacteriaceae increased. Although this family includes probiotic strains, it has been reported as increased in PD [38,51]. Decreases were observed in families containing bacteria that produce LPS and H_2S (Enterococcaceae and Desulfovibrionaceae); metabolites that have been linked to gut barrier dysfunction, inflammation, neuroinflammation, and α-synuclein aggregation [17,41,49,52,87]. Reductions were also noted in Erysipelotrichaceae, a family with strains that have been linked to gastrointestinal disruption [53] and an altered lipid metabolism [54].

Many SCFA-producing genera are reported to be decreased in the PD microbiome compared to HCs (Table 2), including the archetypal SCFA producer *Faecalibacterium,* which has been identified as one of the main producers of butyrate in the gut [88] and has consistently been reported as depleted in PD [56,57,58].

Enrichment of *Faecalibacterium, Bifidobacterium, Turicibacter, Butyricimonas*, and the Ruminococcaceae, as well as other SCFA producers, suggests increased SCFA production in the gut, although production of SCFA is strain-specific [89] and can also be affected by diet, host factors, and the gut environment [90]. The reduction of other SCFA-producing genera (*Roseburia, Coprococcus*, *Eubacterium, Bacteroides, Gemmiger*) underscores the complexity of the changes in the microbiome. The reported enrichment in the PD microbiome of taxa that are, in other contexts considered healthy (*Akkermansia*, *Bifidobacterium, Lactobacillus*) similarly suggests strain-specific and host-specific effects [38,51]. *Akkermansia,* for example, despite supporting mucin production and gut barrier health in some settings [15,81], has been linked to systemic inflammation and symptom progression in some PD studies [38,57] and was reduced in most participants in the present study.

In parallel with these changes in some putative beneficial taxa, there were decreases in *Klebsiella*, *Bilophila*, and *Desulfovibrio*, all of which are commonly enriched in PD dysbiosis [9,39,87], which suggests reduced exposure to LPS and H_2S in the microbiomes of our participants, and may indicate some stabilisation of metabolic risk pathways. A notable exception was the significant increase in *Collinsella,* which has been implicated in increased gut permeability and pro-inflammatory signalling [35] and is reported as associated with PD dysbiosis [36,66], PD progression [35] and Lewy Body dementia [77]. Increases in this genus highlight the need for strain-level and functional profiling, as taxa may exert context-dependent effects [35,83,91,92]. The extremely high proportion of *Enterococcus_B* observed in one participant at 5 years is most likely indicative of an infection or treatment with antibiotics. *Enterococcus faecium*, a notable species in this genus, is commensal in the gut at low levels but is also known as an opportunistic pathogen with multiple antibiotic resistances and can dominate the gut microbiome in response to broad-spectrum antibiotic exposure [93].

The microbiome findings somewhat align with cross-sectional studies that have reported depletion of SCFA producers and enrichment of pro-inflammatory taxa in PD compared to HCs. Taken together, these exploratory taxonomic changes, including increases in the relative proportion of some SCFA producers and reductions in the proportion of several pathobionts, support the hypothesis that, in parallel with clinical stability, PBM might be associated with a shift towards a more metabolically supportive and less pro-inflammatory gut environment. However, alternative explanations for the changes in the microbiome in these participants (such as diet, lifestyle, natural fluctuations, etc.) cannot be excluded.

Notably, the microbiome changes observed in this study differ from the relative stability of the PD microbiome reported in other longitudinal studies [34,94]. However, the decreases in some SCFA-producing genera, including *Roseburia*, and the increases in *Bifidobacterium* and other genera that are reported as increased in PD, together with the marked increase in *Collinsella,* highlight the complexity of interpreting longitudinal microbial shifts.

4.3. Mechanistic Links Between PBM and the Microbiome

The mechanism by which PBM might influence the microbiome remains incompletely defined. In animal models, direct abdominal irradiation has been demonstrated in a number of studies to increase SCFA producers and reduce pro-inflammatory taxa [27,95,96,97,98,99], and direct irradiation of human faecal samples has been reported to restore cryo-damaged microbiota [100]. However, since photon penetration is limited to a few centimetres, light will not reach the interior of the gut in humans and can have no direct effect on the microbiota. Thus, interaction of PBM with the gut microbiome would be indirect. PBM has a well-known anti-inflammatory effect, directly modulating the inflammatory process by reducing pro-inflammatory cytokines (interleukin [IL]-1β, IL-6, Tumor Necrosis Factor alpha [TNF-α]) and increasing anti-inflammatory cytokines (IL-10), as well as modifying pro-inflammatory macrophages (M1) to the anti-inflammatory phenotype (M2) [101]. In addition, in animal models, PBM has been shown to modulate extracellular signal-regulated kinase (ERK), influencing the mitogen-activated protein kinase (MAPK) pathways [102,103], which in turn influences the gut-associated lymphoid tissue (GALT) and reduces local abdominal and mucosal inflammation [104,105,106]. Evidence suggests that reducing inflammation has the effect of enhancing gut barrier integrity [107]. PBM also reduces oxidative stress [104], potentially reversing damage to the gut colonic epithelial cells. Improved gut barrier integrity and reduced inflammation create an environment that favours beneficial taxa such as *Faecalibacterium* while suppressing LPS- and H_2S-producing bacteria. We could hypothesise that this convergence of reduced systemic inflammation, improved barrier function, and ecological shifts may go some way to explain both the observed stability in clinical outcomes and changes in microbial composition in the gut.

4.4. Comparison with Other Microbiome-Targeted Interventions

Other microbiome-targeting strategies in PD, such as diet, prebiotics, probiotics, synbiotics, exercise, and FMT, have produced mixed results. Mediterranean and fibre-rich diets appear protective epidemiologically but show inconsistent benefits after PD onset [108,109]. Prebiotics, probiotics, and synbiotics improve dysbiosis and reduce inflammation in animal models [110], but human trials can show selective microbial changes without a lasting clinical impact [111,112,113]. While moderate exercise is known to improve the microbiome in healthy individuals [114], evidence for this effect in PD is lacking. FMT, while highly effective in animal models, has yielded inconsistent clinical results [115,116], with a recent clinical study showing no consistent improvement in motor or non-motor symptoms with 6 months of FMT [117]. Most interventions, with the possible exception of FMT, are comparatively simple to administer. Compared with these interventions, PBM offers several advantages: it is non-invasive and well-tolerated, has a well-documented safety profile, and has shown lasting improvements in both motor and non-motor symptoms of PD in a number of studies [23,24,25,26].

In an aging non-PD population, the microbiome would be expected to deteriorate, with reduced SCFA-producing bacteria and increased pro-inflammatory bacteria [118,119]. In the PD microbiome, we would not expect an improvement in the gut microbiome over time [120]. The observed parallel clinical improvement in the symptoms of PD and the changes in the microbiome suggest the hypothesis that there may be a link between modulation of the microbiome with PBM, the gut–brain axis, and symptomatic improvement.

5. Limitations

Our study findings should be interpreted with great caution. The very small sample size limits statistical power and generalisability, and individual variation in temporal changes in the microbiome highlights the complexity of host–microbe interactions in PD and limits the extent to which the results can be generalised. Confounding factors that might have contributed to microbiome changes were not closely monitored. Dietary changes, although minimal according to participant responses, might have influenced the microbiome changes. Changes in medication, the effect of aging, and changes in exercise and activity level (made possible by improved Parkinson's symptoms) might also have affected the results. It is also possible that the PBM protocol was not strictly adhered to by the participants, and in fact all participants acknowledged some flexibility in following the treatment regimen but also commented that symptom changes when PBM sessions were missed had prompted renewed adherence to the regimen.

Sequencing was restricted to 16S rDNA rather than metagenomics. 16S rDNA sequencing is inaccurate in species-level identification and cannot track functional changes in the microbiome. Future studies should use whole-metagenome sequencing. In addition, sequencing of samples was undertaken on two occasions (July 2019 for baseline samples and May 2024 for 5-year samples), which reduces the confidence in the significance of α- and β-diversity changes. While the conditions to use PERMANOVA were met, the number of paired samples (six) was towards the lower limit for this statistic. Interpretation of the microbiome changes is also limited by the inherent temporal variability iof the microbiome and the variability of microbiota in our participants and in PD generally.

No analysis of metabolites such as SCFA, H_2S, or inflammatory markers was undertaken, which would have added to this study. In addition, this study would have benefitted from measures of gut integrity, such as zonulin and calprotectin tests. The absence of a control group also leaves placebo and lifestyle effects unresolved. Although the clinical stability over five years is encouraging, a direct causal link to PBM cannot yet be confirmed.

Future Directions

Future studies should include larger, well-controlled randomised trials with extended follow-up, integrating multi-omics approaches such as metagenomics, metabolomics, and immunophenotyping to link microbial function with host responses. Strain-level analysis of *Akkermansia, Bifidobacterium,* and *Collinsella* is particularly important, given their context-dependent roles. Mechanistic work on PBM's interaction with GALT and systemic inflammation and its combination with dietary fibre or probiotics may reveal additive or synergistic benefits.

6. Conclusions

This five-year case series is the longest to date examining PBM outcomes in PD. While exploratory, the results suggest that PBM not only stabilises motor signs, cognitive function, sense of smell, and other non-motor symptoms of PD over an extended period but may also influence the microbiome structure. We might hypothesise that PBM could promote an overall improved microbiome composition and that, while not achieving a completely healthy (eubiosis) microbiome, the resultant microbiome changes might be less inflammatory and more enriched in SCFAs, and the parallel improvement in clinical outcomes might be facilitated via the microbiome-gut–brain axis. Larger, rigorously controlled trials incorporating functional multi-omics are needed to clarify the mechanistic links between microbial activity, host metabolism, and disease modification.

Acknowledgments

The authors would like to acknowledge the invaluable help of Geoffrey Herkes for his neurology expertise, Sharon Tilley for her assistance in developing outcome measures and assessing participants, and Olivia Nassaris of Parkinson's Australia, for her ongoing support.

Supplementary Materials

The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm15010368/s1, Table S1: Parameters of the photobiomodulation devices and treatment used in the study. Table S2: Taxonomic changes over 5 years.

jcm-15-00368-s001.zip (208.6KB, zip)

Author Contributions

B.B., A.L. and H.K. conceptualised this study; B.B. and A.L. determined the methodology; B.B. and A.L. carried out the investigation; B.B. wrote the original draft; A.L., C.M. and H.K. contributed to subsequent drafts. All authors have read and agreed to the published version of the manuscript.

Institutional Review Board Statement

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Griffith University (2018/16, approved 3 February 2018).

Informed Consent Statement

Informed consent was obtained from all subjects involved in this study.

Data Availability Statement

The data presented in this study are openly available in NCBI website. 16S rDNA sequences are available under the NCBI BioProject accession number PRJNA790457.

Conflicts of Interest

B.B. and A.L. are cofounders and shareholders of SYMBYX Pty Ltd., the suppliers of some of the photobiomodulation devices. H.K. and C.M. are also shareholders of SYMBYX Pty Ltd.

Funding Statement

This study was partially funded by the Parkinson's South Australia, the San Foundation and private donations.

Footnotes

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.

References

- 1.*Cheng H.C., Ulane C.M., Burke R.E. Clinical progression in Parkinson disease and the neurobiology of axons. Ann. Neurol. 2010;67:715–725. doi: 10.1002/ana.21995.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 2.*Borghammer P., Van Den Berge N. Brain-First versus Gut-First Parkinson's Disease: A Hypothesis. J. Park. Dis. 2019;9:S281–S295. doi: 10.3233/JPD-191721.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 3.*Holmqvist S., Chutna O., Bousset L., Aldrin-Kirk P., Li W., Björklund T., Wang Z.-Y., Roybon L., Melki R., Li J.-Y. Direct evidence of Parkinson pathology spread from the gastrointestinal tract to the brain in rats. Acta Neuropathol. 2014;128:805–820. doi: 10.1007/s00401-014-1343-6.* [DOI] [PubMed] [Google Scholar]
- 4.*Henderson M.X., Trojanowski J.Q., Lee V.M.-Y. α-Synuclein pathology in Parkinson's disease and related α-synucleinopathies. Neurosci. Lett. 2019;709:134316. doi: 10.1016/j.neulet.2019.134316.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 5.*Boulos C., Yaghi N., El Hayeck R., Heraoui G.N., Fakhoury-Sayegh N. Nutritional risk factors, microbiota and Parkinson's disease: What is the current evidence? Nutrients. 2019;11:1896. doi: 10.3390/nu11081896.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 6.*Kaye J., Gage H., Kimber A., Storey L., Trend P. Excess burden of constipation in Parkinson's disease: A pilot study. Mov. Disord. 2006;21:1270–1273. doi: 10.1002/mds.20942.* [DOI] [PubMed] [Google Scholar]
- 7.*Knudsen K., Krogh K., Østergaard K., Borghammer P. Constipation in Parkinson's disease: Subjective symptoms, objective markers, and new perspectives. Mov. Disord. 2017;32:94–105. doi: 10.1002/mds.26866.* [DOI] [PubMed] [Google Scholar]
- 8.*Marzouk N.H., Rashwan H.H., El-Hadidi M., Ramadan R., Mysara M. Proinflammatory and GABA eating bacteria in Parkinson's disease gut microbiome from a meta-analysis perspective. npj Park. Dis. 2025;11:145. doi: 10.1038/s41531-025-00950-z.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 9.*Romano S., Savva G.M., Bedarf J.R., Charles I.G., Hildebrand F., Narbad A. Meta-analysis of the Parkinson's disease gut microbiome suggests alterations linked to intestinal inflammation. npj Park. Dis. 2021;7:27. doi: 10.1038/s41531-021-00156-z.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 10.*Suresh S.B., Malireddi A., Abera M., Noor K., Ansar M., Boddeti S., Nath T.S. Gut Microbiome and Its Role in Parkinson's Disease. Cureus. 2024;16:e73150. doi: 10.7759/cureus.73150.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 11.*Bai F., You L., Lei H., Li X. Association between increased and decreased gut microbiota abundance and Parkinson's disease: A systematic review and subgroup meta-analysis. Exp. Gerontol. 2024;191:112444. doi: 10.1016/j.exger.2024.112444.* [DOI] [PubMed] [Google Scholar]
- 12.*Park D.G., Kang W., Shin I.-J., Chalita M., Oh H.-S., Hyun D.-W., Kim H., Chun J., An Y.-S., Lee E.J., et al. Difference in gut microbial dysbiotic patterns between body-first and brain-first Parkinson's disease. Neurobiol. Dis. 2024;201:106655. doi: 10.1016/j.nbd.2024.106655.* [DOI] [PubMed] [Google Scholar]
- 13.*Berg D., Postuma R.B., Adler C.H., Bloem B.R., Chan P., Dubois B., Gasser T., Goetz C.G., Halliday G., Joseph L., et al. MDS research criteria for prodromal Parkinson's disease. Mov. Disord. 2015;30:1600–1611. doi: 10.1002/mds.26431.* [DOI] [PubMed] [Google Scholar]
- 14.*Candelli M., Franza L., Pignataro G., Ojetti V., Covino M., Piccioni A., Gasbarrini A., Franceschi F. Interaction between lipopolysaccharide and gut microbiota in inflammatory bowel diseases. Int. J. Mol.*

Sci. 2021;22:6242. doi: 10.3390/ijms22126242. [DOI] [PMC free article] [PubMed] [Google Scholar]
- 15.*Di Vincenzo F., Del Gaudio A., Petito V., Lopetuso L.R., Scaldaferri F. Gut microbiota, intestinal permeability, and systemic inflammation: A narrative review. Intern. Emerg. Med. 2024;19:275–293. doi: 10.1007/s11739-023-03374-w.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 16.*Baldini F., Hertel J., Sandt E., Thinnes C.C., Neuberger-Castillo L., Pavelka L., Betsou F., Krüger R., Thiele I., Consortium N.-P. Parkinson's disease-associated alterations of the gut microbiome predict disease-relevant changes in metabolic functions. BMC Biol. 2020;18:62. doi: 10.1186/s12915-020-00775-7.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 17.*Lin C.-H., Chen C.-C., Chiang H.-L., Liou J.-M., Chang C.-M., Lu T.-P., Chuang E.Y., Tai Y.-C., Cheng C., Lin H.-Y., et al. Altered gut microbiota and inflammatory cytokine responses in patients with Parkinson's disease. J. Neuroinflammation. 2019;16:129. doi: 10.1186/s12974-019-1528-y.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 18.*Metcalfe-Roach A., Finlay B.B. The role of the gut microbiome in Parkinson's disease. Future Neurol. 2025;20:2494981. doi: 10.1080/14796708.2025.2494981.* [DOI] [Google Scholar]
- 19.*Hamblin M.R. Mechanisms and Mitochondrial Redox Signaling in Photobiomodulation. Photochem. Photobiol. 2018;94:199–212. doi: 10.1111/php.12864.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 20.*Maghfour J., Mineroff J., Ozog D.M., Jagdeo J., Lim H.W., Kohli I., Anderson R., Kelly K.M., Mamalis A., Munavalli G., et al. Evidence-based consensus on the clinical application of photobiomodulation. J. Am. Acad. Dermatol. 2025;93:429–443. doi: 10.1016/j.jaad.2025.04.031.* [DOI] [PubMed] [Google Scholar]
- 21.*El Massri N., Johnstone D.M., Peoples C.L., Moro C., Reinhart F., Torres N., Stone J., Benabid A.-L., Mitrofanis J. The effect of different doses of near infrared light on dopaminergic cell survival and gliosis in MPTP-treated mice. Int. J. Neurosci. 2016;126:76–87. doi: 10.3109/00207454.2014.994063.* [DOI] [PubMed] [Google Scholar]
- 22.*Johnstone D.M., el Massri N., Moro C., Spana S., Wang X.S., Torres N., Chabrol C., De Jaeger X., Reinhart F., Purushothuman S., et al. Indirect application of near infrared light induces neuroprotection in a mouse model of parkinsonism—An abscopal neuroprotective effect. Neuroscience. 2014;274:93–101. doi: 10.1016/j.neuroscience.2014.05.023.* [DOI] [PubMed] [Google Scholar]
- 23.*Saltmarche A.E., Hares O., Bicknell B., Liebert A., Naeser M., Ramachandran S., Sykes J., Togeretz K., Namini A., Heller G.Z., et al. Effectiveness of Photobiomodulation to Treat Motor and Non-Motor Symptoms of Parkinson's Disease: A Randomised Clinical Trial with Extended Treatment. J. Clin. Med. 2025;14:7463. doi: 10.3390/jcm14217463.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 24.*Liebert A., Bicknell B., Laakso E.-L., Tilley S., Heller G., Kiat H., Herkes G. Improvements in clinical signs and symptoms of Parkinson's disease using photobiomodulation: A five-year follow-up. BMC Neurol. 2024;24:381. doi: 10.1186/s12883-024-03857-z.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 25.*Herkes G., McGee C., Liebert A., Bicknell B., Isaac A., Kiat H., McLachlan C. A novel transcranial photobiomodulation device to address motor signs of Parkinson's disease: A parallel randomised feasibility study. eClinicalMedicine. 2023;66:102338. doi: 10.1016/j.eclinm.2023.102338.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 26.*Liebert A., Bicknell B., Laakso E.L., Heller G., Jalilitabaei P., Tilley S., Mitrofanis J., Kiat H. Improvements in clinical signs of Parkinson's disease using photobiomodulation: A prospective proof-of-concept study. BMC Neurol. 2021;21:256. doi: 10.1186/s12883-021-02248-y.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 27.*Bicknell B., Liebert A., Johnstone D., Kiat H. Photobiomodulation of the microbiome: Implications for metabolic and inflammatory diseases. Lasers Med. Sci. 2018;34:317–327. doi: 10.1007/s10103-018-2594-6.* [DOI] [PubMed] [Google Scholar]
- 28.*Bicknell B., Liebert A., McLachlan C.S., Kiat H. Microbiome Changes in Humans with Parkinson's Disease after Photobiomodulation Therapy: A Retrospective Study. J. Pers. Med. 2022;12:49. doi: 10.3390/jpm12010049.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 29.*Bicknell B., Saltmarche A., Hares O., Herkes G., Liebert A. Parkinson's disease and the Interaction of Photobiomodulation, the Microbiome, and Antibiotics: A Case Series. Med. Res. Arch. 2024;12:1–12. doi: 10.18103/mra.v12i1.4929.* [DOI] [Google Scholar]
- 30.*Bolyen E., Rideout J.R., Dillon M.R., Bokulich N.A., Abnet C.C., Al-Ghalith G.A., Alexander H., Alm E.J., Arumugam M., Asnicar F., et al. Reproducible, interactive, scalable and extensible microbiome data science using QIIME 2. Nat. Biotechnol. 2019;37:852–857. doi: 10.1038/s41587-019-0209-9.* [DOI]

[PMC free article] [PubMed] [Google Scholar]
- 31.*McDonald D., Jiang Y., Balaban M., Cantrell K., Zhu Q., Gonzalez A., Morton J.T., Nicolaou G., Parks D.H., Karst S.M., et al. Greengenes2 unifies microbial data in a single reference tree. Nat. Biotechnol. 2024;42:715–718. doi: 10.1038/s41587-023-01845-1.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 32.*Vázquez-Baeza Y., Pirrung M., Gonzalez A., Knight R. EMPeror: A tool for visualizing high-throughput microbial community data. Gigascience. 2013;2:2047-2217X-2042-2016. doi: 10.1186/2047-217X-2-16.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 33.*Mandal S., Van Treuren W., White R.A., Eggesbø M., Knight R., Peddada S.D. Analysis of composition of microbiomes: A novel method for studying microbial composition. Microb. Ecol. Health Dis. 2015;26:27663. doi: 10.3402/mehd.v26.27663.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 34.*Aho V.T.E., Pereira P.A.B., Voutilainen S., Paulin L., Pekkonen E., Auvinen P., Scheperjans F. Gut microbiota in Parkinson's disease: Temporal stability and relations to disease progression. eBioMedicine. 2019;44:691–707. doi: 10.1016/j.ebiom.2019.05.064.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 35.*Zhang F., Yue L., Fang X., Wang G., Li C., Sun X., Jia X., Yang J., Song J., Zhang Y., et al. Altered gut microbiota in Parkinson's disease patients/healthy spouses and its association with clinical features. Park. Relat. Disord. 2020;81:84–88. doi: 10.1016/j.parkreldis.2020.10.034.* [DOI] [PubMed] [Google Scholar]
- 36.*Cirstea M.S., Yu A.C., Golz E., Sundvick K., Kliger D., Radisavljevic N., Foulger L.H., Mackenzie M., Huan T., Finlay B.B., et al. Microbiota Composition and Metabolism Are Associated With Gut Function in Parkinson's Disease. Mov. Disord. 2020;35:1208–1217. doi: 10.1002/mds.28052.* [DOI] [PubMed] [Google Scholar]
- 37.*Pavan S., Gorthi S.P., Prabhu A.N., Das B., Mutreja A., Vasudevan K., Shetty V., Ramamurthy T., Ballal M. Dysbiosis of the Beneficial Gut Bacteria in Patients with Parkinson's Disease from India. Ann. Indian Acad. Neurol. 2023;26:908–916. doi: 10.4103/aian.aian_460_23.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 38.*Toh T.S., Chong C.W., Lim S.-Y., Bowman J., Cirstea M., Lin C.-H., Chen C.-C., Appel-Cresswell S., Finlay B.B., Tan A.H. Gut microbiome in Parkinson's disease: New insights from meta-analysis. Park. Relat. Disord. 2022;94:1–9. doi: 10.1016/j.parkreldis.2021.11.017.* [DOI] [PubMed] [Google Scholar]
- 39.*Barichella M., Severgnini M., Cilia R., Cassani E., Bolliri C., Caronni S., Ferri V., Cancello R., Ceccarani C., Faierman S., et al. Unraveling gut microbiota in Parkinson's disease and atypical parkinsonism. Mov. Disord. 2019;34:396–405. doi: 10.1002/mds.27581.* [DOI] [PubMed] [Google Scholar]
- 40.*Cryan J.F., O'Riordan K.J., Sandhu K., Peterson V., Dinan T.G. The gut microbiome in neurological disorders. Lancet Neurol. 2020;19:179–194. doi: 10.1016/S1474-4422(19)30356-4.* [DOI] [PubMed] [Google Scholar]
- 41.*Hill-Burns E.M., Debelius J.W., Morton J.T., Wissemann W.T., Lewis M.R., Wallen Z.D., Peddada S.D., Factor S.A., Molho E., Zabetian C.P., et al. Parkinson's disease and Parkinson's disease medications have distinct signatures of the gut microbiome. Mov. Disord. 2017;32:739–749. doi: 10.1002/mds.26942.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 42.*Rojas-Velazquez D., Kidwai S., Liu T.C., El-Yacoubi M.A., Garssen J., Tonda A., Lopez-Rincon A. Understanding Parkinson's: The microbiome and machine learning approach. Maturitas. 2025;193:108185. doi: 10.1016/j.maturitas.2024.108185.* [DOI] [PubMed] [Google Scholar]
- 43.*Yan Z., Yang F., Cao J., Ding W., Yan S., Shi W., Wen S., Yao L. Alterations of gut microbiota and metabolome with Parkinson's disease. Microb. Pathog. 2021;160:105187. doi: 10.1016/j.micpath.2021.105187.* [DOI] [PubMed] [Google Scholar]
- 44.*Metwaly A., Reitmeier S., Haller D. Microbiome risk profiles as biomarkers for inflammatory and metabolic disorders. Nat. Rev. Gastroenterol. Hepatol. 2022;19:383–397. doi: 10.1038/s41575-022-00581-2.* [DOI] [PubMed] [Google Scholar]
- 45.*Nuzum N.D., Szymlek-Gay E.A., Loke S., Dawson S.L., Teo W.-P., Hendy A.M., Loughman A., Macpherson H. Differences in the gut microbiome across typical ageing and in Parkinson's disease. Neuropharmacology. 2023;235:109566. doi: 10.1016/j.neuropharm.2023.109566.* [DOI] [PubMed] [Google Scholar]
- 46.*Mehanna M., AbuRaya S., Ahmed S.M., Ashmawy G., Ibrahim A., AbdelKhaliq E. Study of the gut microbiome in Egyptian patients with Parkinson's Disease. BMC Microbiol. 2023;23:196. doi: 10.1186/s12866-023-02933-7.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 47.*Hu Y., Wang H., Zhong Y., Sun Y. Retrospective analysis of diet and gut microbiota diversity and*

clinical pharmacology outcomes in patients with Parkinsonism syndrome. Heliyon. 2024;10:e38645. doi: 10.1016/j.heliyon.2024.e38645. [DOI] [PMC free article] [PubMed] [Google Scholar]

- 48.*Scheperjans F., Aho V., Pereira P.A., Koskinen K., Paulin L., Pekkonen E., Haapaniemi E., Kaakkola S., Eerola-Rautio J., Pohja M., et al. Gut microbiota are related to Parkinson's disease and clinical phenotype. Mov. Disord. 2015;30:350–358. doi: 10.1002/mds.26069.* [DOI] [PubMed] [Google Scholar]
- 49.*Munteanu C., Onose G., Rotariu M., Poștaru M., Turnea M., Galaction A.I. Role of Microbiota-Derived Hydrogen Sulfide (H2S) in Modulating the Gut-Brain Axis: Implications for Alzheimer's and Parkinson's Disease Pathogenesis. Biomedicines. 2024;12:2670. doi: 10.3390/biomedicines12122670.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 50.*Bullich C., Keshavarzian A., Garssen J., Kraneveld A., Perez-Pardo P. Gut Vibes in Parkinson's Disease: The Microbiota-Gut-Brain Axis. Mov. Disord. Clin. Pract. 2019;6:639–651. doi: 10.1002/mdc3.12840.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 51.*Li Z., Liang H., Hu Y., Lu L., Zheng C., Fan Y., Wu B., Zou T., Luo X., Zhang X., et al. Gut bacterial profiles in Parkinson's disease: A systematic review. CNS Neurosci. Ther. 2023;29:140–157. doi: 10.1111/cns.13990.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 52.*Murros K.E. Hydrogen Sulfide Produced by Gut Bacteria May Induce Parkinson's Disease. Cells. 2022;11:978. doi: 10.3390/cells11060978.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 53.*Zhou M., Wu J., Wu L., Sun X., Chen C., Huang L. The utilization of N-acetylgalactosamine and its effect on the metabolism of amino acids in Erysipelotrichaceae strain. BMC Microbiol. 2024;24:397. doi: 10.1186/s12866-024-03505-z.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 54.*Zhang N., Peng Y., Zhao L., He P., Zhu J., Liu Y., Liu X., Liu X., Deng G., Zhang Z., et al. Integrated Analysis of Gut Microbiome and Lipid Metabolism in Mice Infected with Carbapenem-Resistant Enterobacteriaceae. Metabolites. 2022;12:892. doi: 10.3390/metabo12100892.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 55.*Lubomski M., Xu X., Holmes A.J., Muller S., Yang J.Y.H., Davis R.L., Sue C.M. Nutritional Intake and Gut Microbiome Composition Predict Parkinson's Disease. Front. Aging Neurosci. 2022;14:881872. doi: 10.3389/fnagi.2022.881872.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 56.*Aho V.T.E., Houser M.C., Pereira P.A.B., Chang J., Rudi K., Paulin L., Hertzberg V., Auvinen P., Tansey M.G., Scheperjans F. Relationships of gut microbiota, short-chain fatty acids, inflammation, and the gut barrier in Parkinson's disease. Mol. Neurodegener. 2021;16:6. doi: 10.1186/s13024-021-00427-6.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 57.*Nishiwaki H., Ito M., Hamaguchi T., Maeda T., Kashihara K., Tsuboi Y., Ueyama J., Yoshida T., Hanada H., Takeuchi I., et al. Short chain fatty acids-producing and mucin-degrading intestinal bacteria predict the progression of early Parkinson's disease. npj Park. Dis. 2022;8:65. doi: 10.1038/s41531-022-00328-5.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 58.*Palacios N., Wilkinson J., Bjornevik K., Schwarzschild M.A., McIver L., Ascherio A., Huttenhower C. Metagenomics of the Gut Microbiome in Parkinson's Disease: Prodromal Changes. Ann. Neurol. 2023;94:486–501. doi: 10.1002/ana.26719.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 59.*Ning J., Huang S.-Y., Chen S.-D., Zhang Y.-R., Huang Y.-Y., Yu J.-T. Investigating Casual Associations Among Gut Microbiota, Metabolites, and Neurodegenerative Diseases: A Mendelian Randomization Study. J. Alzheimer's Dis. 2022;87:211–222. doi: 10.3233/JAD-215411.* [DOI] [PubMed] [Google Scholar]
- 60.*Kang Y., Kang X., Zhang H., Liu Q., Yang H., Fan W. Gut Microbiota and Parkinson's Disease: Implications for Faecal Microbiota Transplantation Therapy. ASN Neuro. 2021;13:17590914211016217. doi: 10.1177/17590914211016217.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 61.*Liu J., Lv X., Ye T., Zhao M., Chen Z., Zhang Y., Yang W., Xie H., Zhan L., Chen L., et al. Microbiota-microglia crosstalk between Blautia producta and neuroinflammation of Parkinson's disease: A bench-to-bedside translational approach. Brain Behav. Immun. 2024;117:270–282. doi: 10.1016/j.bbi.2024.01.010.* [DOI] [PubMed] [Google Scholar]
- 62.*Ewaschuk J.B., Diaz H., Meddings L., Diederichs B., Dmytrash A., Backer J., Looijer-van Langen M., Madsen K.L. Secreted bioactive factors from Bifidobacterium infantis enhance epithelial cell barrier function. Am. J. Physiol.-Gastrointest. Liver Physiol. 2008;295:G1025–G1034. doi: 10.1152/ajpgi.90227.2008.* [DOI] [PubMed] [Google Scholar]
- 63.*Minato T., Maeda T., Fujisawa Y., Tsuji H., Nomoto K., Ohno K., Hirayama M. Progression of Parkinson's disease is associated with gut dysbiosis: Two-year follow-up study. PLoS ONE. 2017;12:e0187307. doi: 10.1371/journal.pone.0187307.* [DOI] [PMC free article] [PubMed] [Google Scholar]

- 64.*Parker B.J., Wearsch P.A., Veloo A.C.M., Rodriguez-Palacios A. The Genus Alistipes: Gut Bacteria With Emerging Implications to Inflammation, Cancer, and Mental Health. Front. Immunol. 2020;11:906. doi: 10.3389/fimmu.2020.00906.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 65.*Wallen Z.D., Demirkan A., Twa G., Cohen G., Dean M.N., Standaert D.G., Sampson T.R., Payami H. Metagenomics of Parkinson's disease implicates the gut microbiome in multiple disease mechanisms. Nat. Commun. 2022;13:6958. doi: 10.1038/s41467-022-34667-x.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 66.*Zeng J., Li Y., Yan J., Chang R., Xu M., Zhou G., Meng J., Liu D., Mao Z., Yang Y. Gut microbiota from patients with Parkinson's disease causes motor deficits in honeybees. Front. Microbiol. 2024;15:1418857. doi: 10.3389/fmicb.2024.1418857.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 67.*Petrov V., Saltykova I., Zhukova I., Alifirova V., Zhukova N., Dorofeeva Y.B., Tyakht A., Kovarsky B., Alekseev D., Kostryukova E., et al. Analysis of gut microbiota in patients with Parkinson's disease. Bull. Exp. Biol. Med. 2017;162:734–737. doi: 10.1007/s10517-017-3700-7.* [DOI] [PubMed] [Google Scholar]
- 68.*Heintz-Buschart A., Pandey U., Wicke T., Sixel-Döring F., Janzen A., Sittig-Wiegand E., Trenkwalder C., Oertel W.H., Mollenhauer B., Wilmes P. The nasal and gut microbiome in Parkinson's disease and idiopathic rapid eye movement sleep behavior disorder. Mov. Disord. 2018;33:88–98. doi: 10.1002/mds.27105.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 69.*Jin M., Li J., Liu F., Lyu N., Wang K., Wang L., Liang S., Tao H., Zhu B., Alkasir R. Analysis of the Gut Microflora in Patients With Parkinson's Disease. Front. Neurosci. 2019;13:1184. doi: 10.3389/fnins.2019.01184.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 70.*Bedarf J.R., Hildebrand F., Coelho L.P., Sunagawa S., Bahram M., Goeser F., Bork P., Wüllner U. Functional implications of microbial and viral gut metagenome changes in early stage L-DOPA-naïve Parkinson's disease patients. Genome Med. 2017;9:39. doi: 10.1186/s13073-017-0428-y.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 71.*Zapała B., Stefura T., Wójcik-Pędziwiatr M., Kabut R., Bałajewicz-Nowak M., Milewicz T., Dudek A., Stój A., Rudzińska-Bar M. Differences in the Composition of Gut Microbiota between Patients with Parkinson's Disease and Healthy Controls: A Cohort Study. J. Clin. Med. 2021;10:5698. doi: 10.3390/jcm10235698.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 72.*Ren T., Gao Y., Qiu Y., Jiang S., Zhang Q., Zhang J., Wang L., Zhang Y., Wang L., Nie K. Gut Microbiota Altered in Mild Cognitive Impairment Compared With Normal Cognition in Sporadic Parkinson's Disease. Front. Neurol. 2020;11:137. doi: 10.3389/fneur.2020.00137.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 73.*Crost E.H., Coletto E., Bell A., Juge N. Ruminococcus gnavus: Friend or foe for human health. FEMS Microbiol. Rev. 2023;47:fuad014. doi: 10.1093/femsre/fuad014.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 74.*Keshavarzian A., Green S.J., Engen P.A., Voigt R.M., Naqib A., Forsyth C.B., Mutlu E., Shannon K.M. Colonic bacterial composition in Parkinson's disease. Mov. Disord. 2015;30:1351–1360. doi: 10.1002/mds.26307.* [DOI] [PubMed] [Google Scholar]
- 75.*Zhang Y., Mo C., He X., Xiao Q., Yang X. Gut microbial community of patients with Parkinson's disease analyzed using metagenome-assembled genomes. Neural Regen. Res. 2025;21:1–11. doi: 10.4103/NRR.NRR-D-25-00420.* [DOI] [PubMed] [Google Scholar]
- 76.*Gomez-Arango L.F., Barrett H.L., Wilkinson S.A., Callaway L.K., McIntyre H.D., Morrison M., Dekker Nitert M. Low dietary fiber intake increases Collinsella abundance in the gut microbiota of overweight and obese pregnant women. Gut Microbes. 2018;9:189–201. doi: 10.1080/19490976.2017.1406584.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 77.*Nishiwaki H., Ueyama J., Kashihara K., Ito M., Hamaguchi T., Maeda T., Tsuboi Y., Katsuno M., Hirayama M., Ohno K. Gut microbiota in dementia with Lewy bodies. npj Park. Dis. 2022;8:169. doi: 10.1038/s41531-022-00428-2.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 78.*Qian H., Zuo Y., Wen S., Wang X., Liu Y., Li T. Impact of exercise training on gut microbiome imbalance in obese individuals: A study based on Mendelian randomization analysis. Front. Physiol. 2023;14:1264931. doi: 10.3389/fphys.2023.1264931.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 79.*Zhang Y., Xu D., Cai X., Xing X., Shao X., Yin A., Zhao Y., Wang M., Fan Y.N., Liu B., et al. Gut Commensal Barnesiella Intestinihominis Ameliorates Hyperglycemia and Liver Metabolic Disorders. Adv. Sci. 2025;12:e2411181. doi: 10.1002/advs.202411181.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 80.*Lubomski M., Xu X., Holmes A.J., Muller S., Yang J.Y., Davis R.L., Sue C.M. The gut microbiome in*

Parkinson's disease: A longitudinal study of the impacts on disease progression and the use of device-assisted therapies. Front. Aging Neurosci. 2022;14:875261. doi: 10.3389/fnagi.2022.875261. [DOI] [PMC free article] [PubMed] [Google Scholar]

- 81.*Lei W., Cheng Y., Gao J., Liu X., Shao L., Kong Q., Zheng N., Ling Z., Hu W. Akkermansia muciniphila in neuropsychiatric disorders: Friend or foe? Front. Cell. Infect. Microbiol. 2023;13:1224155. doi: 10.3389/fcimb.2023.1224155.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 82.*Amorim Neto D.P., Bosque B.P., Pereira de Godoy J.V., Rodrigues P.V., Meneses D.D., Tostes K., Costa Tonoli C.C., Faustino de Carvalho H., González-Billault C., de Castro Fonseca M. Akkermansia muciniphila induces mitochondrial calcium overload and α -synuclein aggregation in an enteroendocrine cell line. iScience. 2022;25:103908. doi: 10.1016/j.isci.2022.103908.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 83.*Xu K., Wang G., Gong J., Yang X., Cheng Y., Li D., Sheng S., Zhang F. Akkermansia muciniphila protects against dopamine neurotoxicity by modulating butyrate to inhibit microglia-mediated neuroinflammation. Int. Immunopharmacol. 2025;152:114374. doi: 10.1016/j.intimp.2025.114374.* [DOI] [PubMed] [Google Scholar]
- 84.*Holden S.K., Finseth T., Sillau S.H., Berman B.D. Progression of MDS-UPDRS scores over five years in de novo Parkinson disease from the Parkinson's progression markers initiative cohort. Mov. Disord. Clin. Pract. 2018;5:47–53. doi: 10.1002/mdc3.12553.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 85.*Pietrucci D., Cerroni R., Unida V., Farcomeni A., Pierantozzi M., Mercuri N.B., Biocca S., Stefani A., Desideri A. Dysbiosis of gut microbiota in a selected population of Parkinson's patients. Park. Relat. Disord. 2019;65:124–130. doi: 10.1016/j.parkreldis.2019.06.003.* [DOI] [PubMed] [Google Scholar]
- 86.*Qian Y., Yang X., Xu S., Huang P., Li B., Du J., He Y., Su B., Xu L.-M., Wang L., et al. Gut metagenomics-derived genes as potential biomarkers of Parkinson's disease. Brain. 2020;143:2474–2489. doi: 10.1093/brain/awaa201.* [DOI] [PubMed] [Google Scholar]
- 87.*Wallen Z.D., Appah M., Dean M.N., Sesler C.L., Factor S.A., Molho E., Zabetian C.P., Standaert D.G., Payami H. Characterizing dysbiosis of gut microbiome in PD: Evidence for overabundance of opportunistic pathogens. npj Park. Dis. 2020;6:11. doi: 10.1038/s41531-020-0112-6.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 88.*Lopez-Siles M., Duncan S.H., Garcia-Gil L.J., Martinez-Medina M. Faecalibacterium prausnitzii: From microbiology to diagnostics and prognostics. ISME J. 2017;11:841–852. doi: 10.1038/ismej.2016.176.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 89.*Frolova M.S., Suvorova I.A., Iablokov S.N., Petrov S.N., Rodionov D.A. Genomic reconstruction of short-chain fatty acid production by the human gut microbiota. Front. Mol. Biosci. 2022;9:949563. doi: 10.3389/fmolb.2022.949563.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 90.*den Besten G., van Eunen K., Groen A.K., Venema K., Reijngoud D.J., Bakker B.M. The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. J. Lipid Res. 2013;54:2325–2340. doi: 10.1194/jlr.R036012.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 91.*Depommier C., Everard A., Druart C., Plovier H., Van Hul M., Vieira-Silva S., Falony G., Raes J., Maiter D., Delzenne N.M., et al. Supplementation with Akkermansia muciniphila in overweight and obese human volunteers: A proof-of-concept exploratory study. Nat. Med. 2019;25:1096–1103. doi: 10.1038/s41591-019-0495-2.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 92.*Ou Z., Deng L., Lu Z., Wu F., Liu W., Huang D., Peng Y. Protective effects of Akkermansia muciniphila on cognitive deficits and amyloid pathology in a mouse model of Alzheimer's disease. Nutr. Diabetes. 2020;10:12. doi: 10.1038/s41387-020-0115-8.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 93.*Donskey C.J., Chowdhry T.K., Hecker M.T., Hoyen C.K., Hanrahan J.A., Hujer A.M., Hutton-Thomas R.A., Whalen C.C., Bonomo R.A., Rice L.B. Effect of antibiotic therapy on the density of vancomycin-resistant enterococci in the stool of colonized patients. N. Engl. J. Med. 2000;343:1925–1932. doi: 10.1056/NEJM200012283432604.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 94.*Cerroni R., Pietrucci D., Teofani A., Chillemi G., Liguori C., Pierantozzi M., Unida V., Selmani S., Mercuri N.B., Stefani A. Not just a snapshot: An Italian longitudinal evaluation of stability of gut microbiota findings in Parkinson's disease. Brain Sci. 2022;12:739. doi: 10.3390/brainsci12060739.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 95.*Chen Q., Wu J., Dong X., Yin H., Shi X., Su S., Che B., Li Y., Yang J. Gut flora-targeted photobiomodulation therapy improves senile dementia in an Aß-induced Alzheimer's disease animal model. J. Photochem. Photobiol. B Biol. 2021;216:112152. doi: 10.1016/j.jphotobiol.2021.112152.* [DOI] [PubMed] [Google Scholar]

- 96.*Min S.H., Kwon J., Do E.-J., Kim S.H., Kim E.S., Jeong J.-Y., Bae S.M., Kim S.-Y., Park D.H. Duodenal Dual-Wavelength Photobiomodulation Improves Hyperglycemia and Hepatic Parameters with Alteration of Gut Microbiome in Type 2 Diabetes Animal Model. Cells. 2022;11:3490. doi: 10.3390/cells11213490.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 97.*Sancho-Balsells A., Borràs-Pernas S., Flotta F., Chen W., Del Toro D., Rodríguez M.J., Alberch J., Blivet G., Touchon J., Xifró X., et al. Brain–gut photobiomodulation restores cognitive alterations in chronically stressed mice through the regulation of Sirt1 and neuroinflammation. J. Affect. Disord. 2024;354:574–588. doi: 10.1016/j.jad.2024.03.075.* [DOI] [PubMed] [Google Scholar]
- 98.*Upadhyay P., Banstola A., Bhayana B., Wu M.X. Photobiomodulation strengthens muscles via its dual functions in gut microbiota. Adv. Sci. 2025;12:e11582. doi: 10.1002/advs.202511582.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 99.*Cao S., Shi X., Chen Y., Liu T., Hu J., Dong X., Chen H., Dai J., Yin H. Gut Microbiota-Targeted Photobiomodulation Ameliorates Alzheimer's Pathology via the Gut–Brain Axis: Comparable Efficacy to Transcranial Irradiation. Microorganisms. 2025;13:2659. doi: 10.3390/microorganisms13122659.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 100.*Khramov R.N., Zalomova L.V., Fesenko E.E., Jr. Study of the Effect of Photobiomodulation on the Human Intestinal Microbiota in vitro During Normal and Post-Cryopreservation. Biophysics. 2025;70:1230–1239. doi: 10.31857/S0006302925060207.* [DOI] [Google Scholar]
- 101.*Cardoso F.D.S., Salehpour F., Coimbra N.C., Gonzalez-Lima F., Gomes da Silva S. Photobiomodulation for the treatment of neuroinflammation: A systematic review of controlled laboratory animal studies. Front. Neurosci. 2022;16:1006031. doi: 10.3389/fnins.2022.1006031.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 102.*Al Balah O.F., Rafie M., Osama A.-R. Immunomodulatory effects of photobiomodulation: A comprehensive review. Lasers Med. Sci. 2025;40:187. doi: 10.1007/s10103-025-04417-8.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 103.*Kang M., Jo J., Shin H., Kang H.W. Therapeutic potential of wavelength-dependent photobiomodulation on gut inflammation in an in vitro intestinal model. J. Photochem. Photobiol. B Biol. 2025;269:113201. doi: 10.1016/j.jphotobiol.2025.113201.* [DOI] [PubMed] [Google Scholar]
- 104.*Hamblin M.R. Mechanisms and applications of the anti-inflammatory effects of photobiomodulation. AIMS Biophys. 2017;4:337–361. doi: 10.3934/biophy.2017.3.337.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 105.*Jiménez-García A.M., Zorzo C., Gutiérrez-Menéndez A., Arias J.L., Arias N. Transabdominal photobiomodulation applications: A systematic review and meta-analysis. Obes. Rev. 2025;26:e13921. doi: 10.1111/obr.13921.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 106.*Yoshimura T.M., Sabino C.P., Ribeiro M.S. Photobiomodulation reduces abdominal adipose tissue inflammatory infiltrate of diet-induced obese and hyperglycemic mice. J. Biophotonics. 2016;9:1255–1262. doi: 10.1002/jbio.201600088.* [DOI] [PubMed] [Google Scholar]
- 107.*Kong C., Yang M., Yue N., Zhang Y., Tian C., Wei D., Shi R., Yao J., Wang L., Li D. Restore Intestinal Barrier Integrity: An Approach for Inflammatory Bowel Disease Therapy. J. Inflamm. Res. 2024;17:5389–5413. doi: 10.2147/JIR.S470520.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 108.*Knight E., Geetha T., Burnett D., Babu J.R. The Role of Diet and Dietary Patterns in Parkinson's Disease. Nutrients. 2022;14:4472. doi: 10.3390/nu14214472.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 109.*Hegelmaier T., Lebbing M., Duscha A., Tomaske L., Tönges L., Holm J.B., Bjørn Nielsen H., Gatermann S.G., Przuntek H., Haghikia A. Interventional Influence of the Intestinal Microbiome Through Dietary Intervention and Bowel Cleansing Might Improve Motor Symptoms in Parkinson's Disease. Cells. 2020;9:376. doi: 10.3390/cells9020376.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 110.*Mirzaei H., Sedighi S., Kouchaki E., Barati E., Dadgostar E., Aschner M., Tamtaji O.R. Probiotics and the Treatment of Parkinson's Disease: An Update. Cell. Mol. Neurobiol. 2021;42:2449–2457. doi: 10.1007/s10571-021-01128-w.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 111.*Lin C.-H., Lai H.-C., Wu M.-S. Gut-oriented disease modifying therapy for Parkinson's disease. J. Formos. Med. Assoc. 2023;122:9–18. doi: 10.1016/j.jfma.2022.09.010.* [DOI] [PubMed] [Google Scholar]
- 112.*Sun H., Zhao F., Liu Y., Ma T., Jin H., Quan K., Leng B., Zhao J., Yuan X., Li Z., et al. Probiotics synergized with conventional regimen in managing Parkinson's disease. npj Park. Dis. 2022;8:62. doi: 10.1038/s41531-022-00327-6.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 113.*Tan A.H., Hor J.W., Chong C.W., Lim S.Y. Probiotics for Parkinson's disease: Current evidence and future directions. JGH Open. 2021;5:414–419. doi: 10.1002/jgh3.12450.* [DOI] [PMC free article]

[PubMed] [Google Scholar]
- 114.*Varghese S., Rao S., Khattak A., Zamir F., Chaari A. Physical Exercise and the Gut Microbiome: A Bidirectional Relationship Influencing Health and Performance. Nutrients. 2024;16:3663. doi: 10.3390/nu16213663.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 115.*Shekar S., Venkatachalapathy R., Jayaraman A., Sai Supra Siddhu N. Fecal microbiota transplantation for Parkinson's disease: A systematic review of clinical evidence. Med. Microecol. 2025;25:100128. doi: 10.1016/j.medmic.2025.100128.* [DOI] [Google Scholar]
- 116.*Cheng Y., Tan G., Zhu Q., Wang C., Ruan G., Ying S., Qie J., Hu X., Xiao Z., Xu F., et al. Efficacy of fecal microbiota transplantation in patients with Parkinson's disease: Clinical trial results from a randomized, placebo-controlled design. Gut Microbes. 2023;15:2284247. doi: 10.1080/19490976.2023.2284247.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 117.*De Sciscio M., Bryant R.V., Haylock-Jacobs S., Day A.S., Pitchers W., Iansek R., Costello S.P., Kimber T.E. Faecal microbiota transplant in Parkinson's disease: Pilot study to establish safety & tolerability. npj Park. Dis. 2025;11:203. doi: 10.1038/s41531-025-01061-5.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 118.*Ghosh T.S., Shanahan F., O'Toole P.W. The gut microbiome as a modulator of healthy ageing. Nat. Rev. Gastroenterol. Hepatol. 2022;19:565–584. doi: 10.1038/s41575-022-00605-x.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 119.*Kim M., Benayoun B.A. The microbiome: An emerging key player in aging and longevity. Transl. Med. Aging. 2020;4:103–116. doi: 10.1016/j.tma.2020.07.004.* [DOI] [PMC free article] [PubMed] [Google Scholar]
- 120.*Kwon D., Zhang K., Paul K.C., Folle A.D., Del Rosario I., Jacobs J.P., Keener A.M., Bronstein J.M., Ritz B. Diet and the gut microbiome in patients with Parkinson's disease. npj Park. Dis. 2024;10:89. doi: 10.1038/s41531-024-00681-7.* [DOI] [PMC free article] [PubMed] [Google Scholar]

Associated Data

This section collects any data citations, data availability statements, or supplementary materials included in this article.

Supplementary Materials

jcm-15-00368-s001.zip (208.6KB, zip)

Data Availability Statement

The data presented in this study are openly available in NCBI website. 16S rDNA sequences are available under the NCBI BioProject accession number PRJNA790457.

Phylum-, family-, and genus-level microbiome changes after 5 years of PBM in a small PD cohort (n = 6). Taxa changes are presented primarily as exploratory, using a 2-fold difference in relative abundance as the threshold for change. Statistical inference using ANCOM identified a significant increase in *Collinsella*.

Taxa	Functional Relevance	Change in PD vs. HCs	Change over 5 Years			Mean % in Microbiome
			Incr.	Decr.	nc nd	
	Phylum					
Bacillota	Contains many SCFA producers	Often depleted [8,10]	2	4	-	17.055
Actinomycetota	Mixed functions, some beneficial		6	0	-	17.550

Bacteroidota	Contains SCFA producers as well as pathobionts	Can be enriched [8,46] or depleted [47]	2	4	-		9.832
Pseudomonadota	Contains many pathobionts	Enriched in PD [48]	2	4	-		0.762
Desulfobacterota	H_2S-producing bacteria	Enriched in PD [49]	1	5	-		0.206
Methanobacteriota	CH_4-producing	Enriched in PD [9]	2	4	-		0.862
		Family					
Ruminococcaceae	Contains SCFA producers	Can be depleted [50] or enriched [11]	3	3	-		7.500
Bifidobacteriaceae	Contains SCFA producers, anti-inflammatory, contains probiotic species	Often enriched [38,51]	5	1	-		12.501
Enterobacteriaceae	Gram-negative, LPS producers, implicated in neuroinflammation	Often enriched [10]	1	2	-	3	0.123
Desulfovibrionaceae	H_2S producers	Enriched [52], linked to α-synuclein aggregation [52]	0	5	1	-	0.205
Erysipelotrichaceae	Contains SCFA producers, increased in inflammatory diseases [53] and disrupted lipid metabolism [54]	Enriched [38] or depleted [55], correlated with worsening UPDRS-III [38]	1	5	-		0.868
		Genus					
		SCFA Producers Reported as Reduced in PD Compared to HCs					
Faecalibacterium	Key SCFA producer, anti-inflammatory, supports gut barrier, reduces systemic and neuroinflammation	Depleted in PD [56,57,58]	4	1	1	-	3.019
Anaerostipes	SCFA producer	Depleted [9], protective against PD [59]	0	2	4	-	2.635
Blautia	SCFA producer	Reduced in PD [60], negatively associated with PD severity [61]	1	2	3	-	13.194
Roseburia_A	SCFA producers, anti-inflammatory, reduces systemic and neuroinflammation	Reduced in PD [60]	0	5	-	1	0.872
Roseburia_C			0	4	-	2	0.149
Ruminococcus_A_187866	SCFA producers, anti-inflammatory		1	2	2	1	0.275
Ruminococcus_A_121497			0	4	0	2	0.265
		SCFA Producers Reported as Increased in PD Compared to HCs					
Bifidobacterium	SCFA producer, enhances tight junctions [62], neuroprotective in other models	Often enriched [8], but low levels found correlated with faster progression [63]	4	0	2	-	12.498
Alistipes	SCFA producer, mixed roles, beneficial and detrimental (IBD) effects [64]	Often enriched [9]	2	4	-	-	1.169
Parabacteroides	SCFA producer, anti-inflammatory in the microbiome	Can be enriched [65]	1	4	1	-	1.486
		SCFA Producers Reported as Either Reduced or Increased in PD Compared to HCs					
Gemmiger	SCFA producer	Sometimes enriched [66], other times depleted	1	3	2	-	3.533
Prevotella	Some strains related to dysbiosis, SCFA producer	Can be depleted [67] or enriched [68], inversely correlated with disease progression [34]	3	0	-	3	0.622

Turicibacter	SCFA producer, modifies bile acids, reduces cholesterol and triglycerides (mice)	Depleted [16] or enriched [69]	4	1		1	0.065
Eubacterium_R	SCFA producers, mixed species	Depleted [70] or enriched [71], some species correlated with higher UPDRS [70]	0	4	1	1	0.630
Eubacterium_J			1	3	-	2	0.364
Eubacterium_G			1	5	-	-	0.163
Eubacterium_F			1	1	1	3	0.083
Eubacterium_I			0	2	2	2	0.078
Butyricimonas	SCFA producers	Enriched in PD [71], higher abundance correlated with worse cognitive symptoms [72] but better non-motor symptoms in one study [45]	4	0	1	1	0.054
Ruminococcus_B	SCFA producers, strain-specific interactions in health and disease [73]	Can be depleted [69] or enriched in PD [42]	0	4	-	2	0.234
Ruminococcus_E			1	3	1	1	0.042
Bacteroides	SCFA producers, some pro-inflammatory strains	Enriched [74] or depleted [67] in PD, low levels correlated with faster progression [63]	2	4	-	-	5.051
Pathobionts—Reported as Enriched in PD Compared to HCs							
Streptococcus	Pathobiont	Enriched in PD [8]	1	0	5	-	2.381
Limiplasma	Unknown	Enriched in PD [9], correlated with PD severity [75]	2	2	1	1	0.375
Collinsella	Related to a high-protein and low-fibre diet [76], may be pro-inflammatory	Enriched in PD in some studies [36,66], depleted in one Indian study [37], related to Lewy Body dementia [77], correlated with faster PD progression [35]	5	1	-	-	3.905
Methanobrevibacter	Archean CH_4 producer	Enriched in PD [9]	0	2	1	3	0.190
Klebsiella	LPS producer	Enriched in PD [65]	1	2	-	3	0.110
Bilophila	H_2S producer	Correlated with PD progression [35]	1	3	-	2	0.059
Desulfovibrio	H_2S producer	Enriched, correlated with worsened MDS-UPDRS-III and IV [38]	0	2	2	2	0.139
Holdemania	Associated with obesity [78]	Over-represented in PD [42]	0	6	-	-	0.054
Other Genera							
Barnesiella	Mixed effects, may ameliorate T2D [79]	Reduced abundance correlated with faster PD progression [80]	3	3		-	0.402
Akkermansia	Mucin degrader, gut barrier support [81]	Often enriched [35], may induce α-synuclein in vitro [82], neuroprotective in a mouse model of PD [83]	2	4	-	-	2.234

PD = Parkinson's disease; HCs = healthy controls; SCFA = short-chain fatty acid; MDS-UPDRS = Movement Disorder Society Unified Parkinson's disease Rating Scale; nd = not detected; nc = no change.