Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Associations between diet and microbiome in Parkinson's disease: a systematic review of evidence and methodological challenges

Emily C. Hoedt

Emily.Hoedt@newcastle.edu.au

University of Newcastle, Australia https://orcid.org/0000-0003-2715-7588

Kerith R. Duncanson

University of Newcastle, Australia https://orcid.org/0000-0001-5525-6589

Nicole M. Simm

University of Newcastle, Australia https://orcid.org/0009-0009-1910-4479

Georgina M. Williams

University of Newcastle, Australia https://orcid.org/0000-0001-7089-3527

Nicholas J. Talley

nicholas.talley@newcastle.edu.au

University of Newcastle, Australia https://orcid.org/0000-0003-2537-3092

Systematic Review

Keywords: Parkinson's disease, diet, microbiome

Posted Date: June 9th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9962008/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: The authors declare potential competing interests as follows: EH, KD, NS and GW have no disclosures to report. NJT: Disclosures: Brown University & Agency for Health Care Research and Quality (fiber and laxation), Rome Foundation (member gastroduodenal committee), Biocodex (FD diagnostic tool), Microba (microbiome), Comvita Manuka Honey (FD trial consulting), Anatara Lifescience (Scientific Advisory Board), BluMaiden (microbiome), Schwabe (FD/IBS), Abbott (prokinetics) outside the submitted work. In addition, Dr. Talley has Licensing Questionnaires: Nepean

Dyspepsia Index (NDI) 1998 licensed to MAPI, Talley Bowel Disease Questionnaires licensed to Mayo Clinic. Patents: “Diagnostic marker for functional gastrointestinal disorders” Australian Provisional Patent Application 2021901692, “Methods and compositions for treating age-related neurodegenerative disease associated with dysbiosis” US Patent Application No. 63/537,725, “Compositions and methods for the treatment of oesophageal disorders” Australian Provisional Patent ID 2025902002. Boards: Asia Pacific Association of Medical Editors (APAME) Board (President 2023-2026), Doctors for the Environment (Chair 2024-2026), Gastroenterological Society of Australia (GESA) Board (2025-2027). Editorial: UptoDate (Section Editor), Mayo Clinic Proceeding Associate Editor (2023-present). Financial support: Dr. Talley is supported by funding from the National Health and Medical Research Council (NHMRC) to the Centre for Research Excellence in Transforming Gut Health.

Abstract

Diet is a major determinant of gut microbiome composition and function, yet its role in Parkinson's disease (PD) microbiome research remains poorly characterised. Despite strong biological plausibility, the extent to which diet contributes to observed microbiome alterations in PD is unclear due to limited and methodologically inconsistent investigation. This systematic review is to evaluate literature that investigates associations between diet and the gastrointestinal microbiome in PD.

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the loss of dopamine-producing neurons in the substantia nigra region of the brain. PD is devastating and relentlessly progressive, impacting approximately 1 in 660 people globally in 2021 with this number projected to rise to 1 in 375 by 2050[1], and prevalence increases with age affecting 1 in 100 over the age of 60 years[2]. The pathophysiology of PD is complex and involves the accumulation of alpha-synuclein protein in the substantia nigra, which forms Lewy bodies and leads to the death of dopamine-producing cells[3]. This loss of neurons leads to the development of tremors, stiffness, slow movement, impaired balance and coordination, and cognitive decline. Braak *et al.*[4] have hypothesized that α-synuclein pathology may arise and progress from the gastrointestinal (GI) tract enteric nervous system to the brain via vagal (gut-brain axis) or alternatively via olfactory (brain-gut) pathways[5], and a growing body of evidence supports this concept[6].

PD often first manifests with GI symptoms that meet Rome criteria for disorders of gut-brain interactions (DGBI)[7,8]. DGBIs are a group of conditions affecting 40% of the world's population across the lifespan[8–13]. Key examples include chronic idiopathic constipation or irritable bowel syndrome (IBS), defined by chronic abdominal pain and altered defaecation[9,10], which frequently overlaps with functional dyspepsia, characterised by early satiety, postprandial fullness, and epigastric pain[11–13]. Psychological comorbidities, including anxiety, depression, and sleep disturbance, commonly arise following symptom onset, highlighting the importance of gut-brain signalling pathways[14,15]. Braak's hypothesis is consistent with the finding that a majority of people with PD experience chronic GI symptoms including chronic idiopathic constipation as well as GI motor disorders such as gastroparesis[16], and other non-motor symptoms such as sleep and mood disorders, and fatigue[17–19]. Patients with chronic constipation have an increased risk of later being diagnosed with PD (OR = 6.5, 95% CI 2.9–14.4)[20], and in over 24,000 PD cases vs. healthy controls, IBS-Constipation was strongly associated with PD (OR = 4.11, 95% CI 2.06–8.20)[6]. Constipation affects more than 80% of individuals with PD, and tends to be chronic, severe, and often doesn't respond to standard therapy, and therefore negatively impacts on quality of life[21]. Colonic symptoms often precede the onset of the central nervous system (CNS) symptoms, sometimes by decades[6,20]. GI dysfunction contributes to not only symptom burden but may alter treatment efficacy, including levodopa responsiveness, through disrupted gut physiology[22,23].

There is an increasing body of evidence to suggest that alterations in the GI microbiome may be associated with the development and progression of PD[24–26]. Studies have shown that people with PD exhibit reduced abundance of short-chain fatty acid (SCFA)-producing taxa (e.g., *Faecalibacterium*, *Roseburia*) and increased levels of potential pathobionts (e.g., Enterobacteriaceae), alongside altered functional capacity compared to healthy individuals[27]. Primarily metabolic microbiome alteration supports the reduction of SCFAs, which is produced by microbial fermentation of dietary fibre, and are important for maintaining colonic health by promoting epithelial integrity, regulating inflammation, and stimulating gut motility[28–30]. Evidence for the GI microbiome-SCFA-motility axis and its role in constipation by impairing colonic transit, reducing stool bulk, and secretion[31] highlights that this is likely a contributor to PD GI symptoms. Furthermore, a recent metagenomic study comparing PD, IBS-C, and healthy controls found that while taxonomic composition differed between PD and IBS-C, however there was substantial overlap in microbial functional capacity, with reductions in pathways related to tryptophan metabolism, polyamine production, and vitamin B biosynthesis in PD, highlighting shared but distinct gut-brain axis alterations between IBS and PD[32].

The current standard of care for PD includes dopamine replacement therapy (i.e., levodopa) along with adjunct pharmacological treatments that primarily target motor symptom control rather than underlying disease progression[33]. However, there is a substantial unmet medical need for PD treatments that can slow or halt disease progression, including better addressing non-motor GI symptoms. Diet is now established as a critical factor shaping the GI microbiome composition[34,35]. The influence of dietary intake on PD may include altering GI motility, driving or ameliorating GI symptoms, and modulating treatment efficacy. Emerging evidence suggests the Mediterranean diet may reduce risk, and delay onset or progression of PD, potentially through anti-inflammatory effects, modulation of the gut microbiome toward short-chain fatty acid-producing taxa, and downstream impacts on gut-brain axis signalling, intestinal barrier integrity, and dopaminergic neurodegeneration[34,36]. While diet and the GI microbiome are both implicated across all stages of PD, and intrinsically linked to each other, we have noticed their relative and complementary influences are rarely explored simultaneously in PD studies. Therefore, despite strong emerging interest in microbiome-targeted therapies, including pre-, pro-, and synbiotics[37], clinical translation may currently be limited by poor study quality and inadequate integration of diet and microbiome biology. Therefore, the aim of this systematic review is to amalgamate and critically evaluate the existing human literature investigating the relationships between whole diet, the GI microbiome, and PD. Specifically, we aim to (i) characterise the dietary assessment methods used to examine whole diet-microbiome interactions in PD studies, (ii) summarise the microbiome sequencing and analytical approaches employed, and (iii) identify and compare reported associations between dietary factors and gut microbiome composition and function in individuals with PD. Additionally, we aim to evaluate the consistency and methodological quality of the evidence to inform future research and the development of targeted dietary or microbiome-based interventions in PD.

Methods

Search strategy

This review extends the methodology and screening framework established in a previous systematic review[35], with further data extraction specific to microbiome-diet associations in PD studies. The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[38]. Briefly, we employed a structured search strategy, based on a previously published review, across MEDLINE, EMBASE, CINAHL, Cochrane CENTRAL register and Google Scholar. Records were deduplicated using EndNote and Covidence, yielding 25,836 studies for screening. An initial search was performed on 20 February 2024 and updated through to 06 May 2026 (Fig. 1). This systematic review has been registered with PROSPERO under identifier CRD420261404668.

To determine diet-microbiome signal consensus in studies that used comparable methodological approaches, our systematic review included studies that reported nutrient composition from whole dietary intakes (at one or more timepoints) of adults with PD and reported on associative microbiome analysis. We systematically searched for original research papers that reported metrics of both dietary intake and the GI microbiome (using either 16S rRNA or metagenomic shotgun sequencing (MGS)) and diet-microbiome associative analysis (i.e., Spearman, MaAsLin, LEfSe, linear regression) in PD populations. Studies were excluded if they reported incomplete dietary intake data (did not analyse all food and drinks consumed) or reported that participants were asked not to change diet in the intervention, but dietary data were not reported. Two reviewers independently screened titles and full text articles for eligibility, with discrepancies checked by a third reviewer. We then screened the nine included studies for a subset with comparable and high-quality methodological approaches that included analysis of nutrient composition, microbiome sequencing via Illumina platforms and statistical methods of either linear regression, linear modelling methods, or MaAsLin2; a specialised implementation of multivariable linear modelling. We identified one study that fitted the associative microbiome-diet analysis criterion which were further extracted to detail the associations between specific nutrient components and microbes at any taxonomic level. Directionality and effect sizes were not consistently available or extractable, so associations were required to be reported as significant p-values and indication of whether the association was positive or negative. Studies included PD cohorts or case control studies to explore where relationships between microbes and dietary substrates were dependent or independent of disease state. Risk of bias was assessed independently by two reviewers using Newcastle-Ottawa Scale, with discrepancies resolved by consensus (**Table S1**). Data were tabulated in Excel then converted to word documents for manuscript preparation.

Declaration of AI-assisted technologies in the manuscript preparation

During the preparation of this manuscript the authors used M365 Copilot to improve the language of some sections. After using this tool/service, the authors reviewed and edited the content as needed and we take full responsibility for the content of the published article.

Results

Extracted studies overview

A total of nine studies met the final inclusion criteria (**Table S2**)[29,39-46], comprising a mix of observational (cross-sectional, case-control, and cohort) and interventional designs across diverse geographic settings (USA, South Korea, China, Taiwan, Germany, Chile, and Colombia). Sample sizes ranged from small pilot cohorts (n=5 to 20) to larger observational studies (n=173), with most populations consisting of older adults with PD and mixed-gender cohorts. Study quality was rated as good for six studies, fair for one study and poor for two studies (**Table S2**).

Dietary assessment was predominantly conducted using food frequency questionnaires (FFQs; 5/9 studies)[39-41,43,44], with 5/9 studies reporting using validated dietary assessment tools (e.g., DHQ-II, Korean FFQ, MEDAS)[39,41,43,44,46], while others reported dietary patterns[45], food logs[29], or a diet quality questionnaire[42]. Most studies [29,39-44,46]. One study analysed both 24 hour recall and FFQ data[43]. Interventional studies primarily examined prebiotic or high-fibre supplementation (**Table S2**).

Microbiome analysis varied across studies (**Table S2**) with 5/9 studies utilising 16S rRNA sequencing[39-43] or metagenomic shotgun sequencing (5/9 MGS studies[29,39,44-46], 1 study using both 16S and MGS[39]). The Illumina sequencing platforms were used in 8/9 studies[29,41,43-46], with 1 study using the BGISEQ-500RS platform[45]. Sample collection was typically based on single stool samples, although four intervention studies included repeated sampling over time[29,42,45,46]. Bioinformatic pipelines and taxonomic annotation approaches differed substantially. Data availability was variable, with several studies providing access to raw sequencing data via online repositories (6/9 studies)[29,41,43-46], while dietary data were less consistently available (2/9 available upon request)[39,41].

Differential statistical approaches to uncover diet-microbiome associations

Across the nine studies, a range of analytical methods were used to investigate associations between dietary intake and the gut microbiome in PD populations, reflecting substantial methodological variability (**Table S2**). Multivariable linear modelling was employed in one study [41], using MaAsLin2, enabling adjustment for potential confounders and identification of taxa associated with dietary exposures. Two studies[39,40] applied Spearman correlation analysis to assess pairwise associations between dietary variables and microbial taxa, representing a more exploratory, non-parametric approach. Multivariate ecological method was also utilised in one study[29], distance-based redundancy analysis (dbRDA) to examine the relationship between dietary factors and overall metagenomic composition, but this was limited in relation to the specific outputs of taxa associated with the prebiotic supplement. In contrast, 3/9 studies[29,42,46] focused on relative abundance analyses, assessing changes in microbial taxa in relation to study groups. Less conventional approaches were observed in one study[45], including

reference-free metagenomic analysis based on k-mer density distributions with UMAP dimensionality reduction.

Notably, two studies[43,44] did not clearly report the statistical methods used to compare dietary intake to microbiome outcomes, limiting comparability across studies (**Table S2**). Overall, there was high heterogeneity in analytical frameworks, including differences in adjustment for confounders, level of taxonomic resolution, and treatment of dietary exposures. This variability in the reporting of diet-microbiome associations negated the possibility of meta-analysis.

Diet-microbiome associations identified using multivariate and non-parametric analyses

Three interventional studies[29,42,46] investigated the impact of prebiotic supplementation on the gut microbiome in PD populations using multivariate/univariate testing and Wilcoxon signed-rank analyses (**Table 1**). Bedarf *et al.* [29] found supplementation with lactulose syrup was associated with a marked increase in multiple *Bifidobacterium* species and UMGS1975 (Christensenellales), suggesting broader ecosystem shifts toward taxa often linked with metabolic health. In contrast, *Streptococcus thermophilus* showed a negative association following intervention. García-Milla *et al.*[42] observed inulin supplementation was associated with reductions in several taxa, including Firmicutes, Verrucomicrobia, *Bifidobacterium*, and *Agathobacter* (**Table 1**). Similarly, oligofructose exposure was linked to decreases in Enterorhabdus, Bacteroidetes, Euryarchaeota, Proteobacteria, and Verrucomicrobia, while Firmicutes showed a positive association. Finally, Hall *et al.*[46] employed a short-term prebiotic bar intervention (containing starch, rice bran, resistant maltodextrin, and inulin) that resulted in decreases in Proteobacteria, including *Escherichia coli*, alongside reductions in *Ruminococcus bromii* and *Ruminococcus torques* (**Table 1**). Concurrently, increases were observed in *Fusicatenibacter saccharivorans*, *Parabacteroides merdae*, *Faecalibacterium prausnitzii*, *Bifidobacterium adolescentis*, and *Ruminococcus bicirculans*. These shifts suggest enrichment of short-chain fatty acid-producing and commensal taxa following prebiotic intake. Overall, prebiotic interventions consistently demonstrated the capacity to modulate the gut microbiome in PD, most notably through increasing beneficial taxa such as *Bifidobacterium* and *Faecalibacterium* and reducing potentially pathogenic or inflammation-associated taxa such as Proteobacteria. However, responses varied depending on the specific prebiotic compound and analytical approach, with some interventions producing mixed or taxon-specific effects.

Diet-Microbiome associations identified using Spearman correlation analysis

Two studies[39,40] focusing on observational case-control design used Spearman correlation analysis to explore associations between dietary variables and gut microbial taxa in PD (**Table 2**). Despite differences in dietary variables assessed, several consistent patterns emerged linking micronutrients, fibre, and fat intake with distinct microbial signatures. In Yoon *et al.*[39], multiple micronutrients and dietary components were associated with taxa typically considered beneficial. Fluorine intake was positively correlated with *Bifidobacterium*, while molybdenum and soluble fibre were both inversely associated with *Lactobacillus*. In contrast, *Faecalibacterium* spp. showed consistent positive

associations with nutrient intake (fluorine fatty acids, manganese and cobalt). Further subgroup analyses revealed PD only associations between aromatic amino acid intake and *Bifidobacterium* (positive), and taurine with *Lactobacillus* (negative). In control-only analyses, long-chain fatty acids (eicosadienoic, eicosatrienoic, and eicosenoic acids) were positively associated with *Faecalibacterium* GG697149.

In Li et al. (2019)[40], macronutrient intake associations were examined (**Table 2**). Dietary fibre was positively associated with unidentified Actinobacteria, but showed negative correlations with multiple taxa, including Deltaproteobacteria, Desulfovibrionales, Desulfovibrionaceae, *Roseburia inulinivorans*, and *Prevotella copri*. Dietary fat intake demonstrated predominantly positive associations, including with unidentified Actinobacteria, the OPB35 soil group, Bifidobacteriales, Corynebacteriales, *Bifidobacterium*, and *Streptococcus mutans*. This pattern suggests that higher fat intake may favour both commensal and potentially pathogenic taxa, indicating a heterogeneous microbial response.

Overall, the two studies[39,40] utilising Spearman correlation analyses highlighted nutrient-specific associations with individual taxa, with consistent enrichment of *Faecalibacterium* and *Bifidobacterium* observed across multiple dietary exposures. However, findings varied by nutrient type and study, underscoring the exploratory nature of correlation-based approaches and the context-specific nature of diet-microbiome relationships in PD.

Multivariable linear modelling specific diet-microbiome associations

Only one[41] of the nine extracted studies used multivariable linear modelling (MaAsLin2) approaches to interrogate diet-microbiome associations, adjusting for age, sex, race, and platform (**Table 3**). Kwon *et al.*[41] identified several significant associations between habitual dietary intake and gut microbial taxa in individuals with Parkinson's disease. Higher dietary fibre intake (g/day) was positively associated with the relative abundance of *Butyricicoccus*, *Coprococcus* 1, *Hydrogenoanaerobacterium*, and *Negativibacillus*, as well as members of the *Parabacteroides* NK4A214 group. In contrast, fibre intake was negatively associated with *Bacteroides* and *Parabacteroides*. Kwon *et al.*[41] further reported associations with dietary sugars (specifically added sugar intake), inverse associations were observed with *Catenibacterium*, *Eubacterium*, and *Streptococcus*, while a positive association was identified with Lachnospiraceae CAG-127 sp. Of all the reported diet-microbiome associative analysis multivariable linear modelling (i.e., MaAsLin2) provides the most robust and interpretable framework, as it enables adjustment for confounding variables and simultaneous assessment of complex diet-microbiome interactions, thereby offering greater reproducibility and biological relevance compared to univariate or correlation-based approaches.

Microbial functional pathways associated with diet

Functional profiling in respect to diet profile or dietary intervention (**Table S3**) was completed in only 4/9 studies and revealed distinct, intervention-specific alterations in microbial metabolic potential. Of these

3/4 studies[29,45,46] employed Wilcoxon signed-rank testing while one study[41] used Multivariable Linear Modelling (MaAsLin2).

Bedarf *et al.* [29] utilised a lactulose supplementation (Day 28 intervention) and the MGS Wilcoxon signed-rank test of KEGG modules reported 19 shared pathways altered in controls and PD, 21 pathways altered in PD only, and 7 pathways altered only for control subjects (**Table S3**). Increased relative abundance was observed in pathways related to carbohydrate transport (multiple sugar transport systems), fatty acid biosynthesis, tetrahydrofolate biosynthesis, and the oxidative pentose phosphate pathway, alongside enhanced RNA processing capacity. In contrast, energy metabolism and cofactor-related pathways, including pyruvate oxidation, acetogenesis, formaldehyde assimilation, and cobalamin biosynthesis, were reduced. In PD specifically, lactulose elicited additional increases in amino acid biosynthesis (serine, threonine) and transport systems, as well as nucleotide precursor and redox-related pathways (e.g., PRPP and glutathione biosynthesis), while glycolysis, sulfur assimilation, and ion transport systems declined, indicating a shift away from core energy metabolism.

Hall *et al.*[46] also employed Wilcoxon signed-rank testing to determine differential MetaCyc MGS pathways following a PD only 10 day intervention with a prebiotic bar (starch, rice brain, resistant maltodextrin, and inulin; **Table S3**). Hall *et al.* reported a reduction in 64 MetaCyc pathways analysis showed a widespread reduction in functional capacity, with decreases spanning nucleotide biosynthesis and salvage, amino acid biosynthesis (including methionine, lysine, and branched-chain amino acids), and cofactor production pathways. Central carbon metabolism (glycolysis and glucose degradation), fermentation (including butanoate production), and cell structural pathways (e.g., peptidoglycan and membrane lipid biosynthesis) were also reduced, indicating a global contraction of microbial metabolic activity.

In contrast, Becker *et al.*[45] Wilcoxon signed-rank testing of differential MetaCyc MGS pathways reported no significant functional changes following an 8-week resistant starch supplementation in either PD or control subjects.

Only one study[41] completed a cross-sectional analysis of habitual diet and MGS functional data (MetaCyc; **Table S3**). Kwon *et al.* utilised MaAsLin2 (adjusted for age, sex, race, and platform) and demonstrated that higher diet quality (HEI) and fibre intake were consistently associated with reduced lipopolysaccharide biosynthesis and decreased formaldehyde assimilation pathways, alongside selective alterations in cofactor metabolism.

Discussion

Despite growing interest in the GI microbiome in PD, the evidence base linking diet, microbiome composition, and clinical outcomes remains fragmented and insufficient to guide therapeutic development. Our systematic review identified only nine studies[29,39–46] that examined diet-microbiome interactions in PD using best practice whole dietary assessment and microbiome analytic methods. Even

in this subset, substantial heterogeneity existed across all aspects of study design, dietary assessment, microbiome methodology, and analytical approaches. Notably, overlap of microbiome functional capacity across datasets was limited; however, consistent signals included modulation of carbohydrate utilisation pathways and reductions in pro-inflammatory or fermentation-related functions (e.g., lipopolysaccharide (LPS) biosynthesis and formaldehyde assimilation), suggesting convergent functional shifts despite differing interventions. Collectively, these findings indicate that microbial functional responses are highly dependent on substrate type and exposure duration, with PD cohorts exhibiting greater functional perturbation than controls.

Diet-microbiome associations identified in this review that were consistent with previous literature included the enrichment of SCFA-associated taxa (e.g., *Faecalibacterium*, *Bifidobacterium*, *Coprococcus*, *Butyricicoccus*). These correlations are well-established in human dietary studies, where fibre- and polyphenol-rich diets consistently increase SCFA-producing genera including *Faecalibacterium* and *Bifidobacterium*[47], and prebiotic supplementation enhances SCFA production while promoting beneficial taxa and suppressing potentially pathogenic organisms[48]. These findings are further supported by mechanistic evidence showing that SCFA-producing bacteria such as *Coprococcus* are directly linked to fibre fermentation and colonic health and neurological disorders[49]. These patterns align with findings reported in other GI and metabolic conditions, including functional constipation and IBS, where fibre intake and microbiota-derived metabolites play key roles in shaping microbial ecology and gut function[31,50,51]. Functional analyses further supported these compositional findings, with higher diet quality and fibre intake associated with reduced LPS biosynthesis and other pro-inflammatory or fermentation-related pathways[52], suggesting consistent shifts toward a less inflammatory microbial functional profile in PD. However, several associations were heterogeneous or inconsistent across studies, particularly for macronutrients such as dietary fat and micronutrients, which demonstrated both positive and negative relationships with taxa such as *Bifidobacterium*, *Lactobacillus*, and Actinobacteria. These inconsistencies likely reflect differences in dietary context, variation in analytical approaches, and the complexity of diet-microbiome interactions, especially in PD where slow transit constipation and nutrient-drug interactions prevail[22]. Importantly, some macronutrient and micronutrient associations may reflect underlying dietary patterns or food compounds rather than isolated nutrient effects. For example, vitamin C intake may act as a proxy for higher consumption of fruits and vegetables, and therefore co-vary with dietary fibre, polyphenols, and lower intake of discretionary foods, all of which independently influence microbial composition and function.

Key limitations we identified included inconsistent dietary assessment methodologies, often relying on tools not designed to capture microbiome-relevant exposures; variable and non-standardised microbiome pipelines across sequencing platforms and bioinformatic workflows; and a predominance of cross-sectional analyses, which preclude causal inference. Additionally, most studies employed simplistic or exploratory statistical approaches (e.g., Spearman correlations or univariate tests), frequently without adequate adjustment for confounders, limiting the reproducibility and interpretability of findings. Critically, poor data transparency, particularly the lack of publicly available dietary datasets,

further restricts cross-study integration and validation. As a result, the current literature provides largely non-comparable findings, preventing synthesis into actionable biological insight and substantially limiting progress toward rational design of microbiome-targeted therapies.

Only one study[41] employed appropriate diet-microbiome associative analysis that accounted for confounders. Therefore, a recommendation is for all future studies to utilise multivariable linear modelling approaches (e.g., MaAsLin2), which enable a more robust interrogation of diet-microbiome relationships by accounting for collinearity. This would markedly improve comparability across studies and support the identification of reproducible, biologically meaningful associations. However, improving statistical approaches alone is insufficient to advance the field. Current studies remain largely limited to associative analyses, primarily based on taxonomic profiling through 16S or metagenomic sequencing. While these approaches identify the compositional "potential" of the microbiome, they do not capture functional activity at the time of sampling. To meaningfully progress towards therapeutic development, particularly for GI symptoms and cognitive decline in PD, future research must move beyond taxonomic associations and incorporate functional multi-omics, including metatranscriptomics and metabolomics. These approaches are essential to interrogate the active metabolic outputs of diet-microbiome interactions and work towards understanding their downstream effects on host physiology.

Similarly, advancements in dietary assessment and analysis are imperative to progress GI microbiome-targeted dietary modulation in PD. Dietary intake needs to be accurately recorded and assessed, factoring in microbiome-relevant dietary variables such a polyphenols and fibre characteristics, and also the temporal relationship between the dietary assessment method and microbiome sampling. These data then need to be analysed in relation to GI symptoms, stool form and frequency in order to inform microbiome-specific PD dietary guidance.

Principles for an optimal diet-microbiome trial in Parkinson's Disease

To support the development of effective dietary and synbiotic interventions, a step-change in study design is required. Future trials should incorporate:

1. Deep, standardised multi-omic phenotyping

Studies must integrate high-resolution dietary assessment capable of capturing microbiome-relevant nutrients, alongside shotgun metagenomics, metatranscriptomics, metabolomics, immune profiling, and detailed clinical phenotyping. This enables modelling of causal pathways linking diet-microbiome-metabolome-host response-symptoms, rather than relying on descriptive associations.

2. Longitudinal, interventional study design

Cross-sectional approaches should be replaced by longitudinal and interventional designs incorporating baseline stabilisation, controlled dietary or synbiotic interventions, and repeated sampling. This allows

assessment of microbiome responsiveness, temporal dynamics, and inter-individual variability.

3. Integration of diet into microbiome modelling

Diet should no longer be treated as a secondary variable. Instead, dietary exposures must be quantified at comparable resolution to microbiome data and incorporated directly into analytical models. Advanced multivariate and machine learning approaches should be used to identify predictive diet-microbiome-metabolome signatures. Dietary data collection should include assessment of dietary intake proximal to stool sampling using at least two days of multiple pass 24-hour recalls, and usual intake collected using a FFQ or diet quality tool.

4. Clinically meaningful endpoints

Future studies should prioritise endpoints directly relevant to PD, including GI symptoms (e.g., constipation, transit), levodopa responsiveness, and patient-reported outcomes, ensuring that microbiome findings are clinically translatable.

5. Data transparency and reproducibility

Open access to raw dietary, microbiome, and clinical datasets, alongside fully reproducible analysis pipelines, is essential to enable cumulative science and overcome the current fragmentation of the field.

Adherence to these principles would enable a transition from exploratory, association-driven studies to mechanism-based intervention design. Leveraging existing capabilities within the investigator team, including advanced dietary assessment, provides a clear opportunity to design next-generation PD diet-microbiome trials that integrate diet, microbiome, and host biology at sufficient resolution. Such an approach would allow identification of microbial pathways responsive to specific dietary inputs, mapping of functional outputs (e.g., SCFA production, bile acid metabolism), and stratification of patients based on diet-microbiome phenotypes. This framework is critical for the rational development of targeted dietary and synbiotic therapies, rather than relying on empirical or generic interventions.

In conclusion, this systematic review demonstrates that while emerging evidence supports meaningful interactions between diet and the gut microbiome in PD, significant heterogeneity across study designs and analytical approaches limits comparability and synthesis. Collectively, advancing the field will require a shift toward standardised, multivariable analytical frameworks alongside integrated multi-omic and longitudinal study designs, enabling progression from largely descriptive microbiome research toward mechanistically informed, clinically actionable dietary and microbiome-targeted interventions in PD.

Declarations

Disclosure of potential conflicts of interest

EH, KD, NS and GW have no disclosures to report.

NJT: Disclosures: Brown University & Agency for Health Care Research and Quality (fiber and laxation), Rome Foundation (member gastroduodenal committee), Biocodex (FD diagnostic tool), Microba (microbiome), Comvita Manuka Honey (FD trial consulting), Anatara Lifescience (Scientific Advisory Board), BluMaiden (microbiome), Schwabe (FD/IBS), Abbott (prokinetics) outside the submitted work. In addition, Dr. Talley has Licensing Questionnaires: Nepean Dyspepsia Index (NDI) 1998 licensed to MAPI, Talley Bowel Disease Questionnaires licensed to Mayo Clinic. Patents: “Diagnostic marker for functional gastrointestinal disorders” Australian Provisional Patent Application 2021901692, “Methods and compositions for treating age-related neurodegenerative disease associated with dysbiosis” US Patent Application No. 63/537,725, “Compositions and methods for the treatment of oesophageal disorders” Australian Provisional Patent ID 2025902002. Boards: Asia Pacific Association of Medical Editors (APAME) Board (President 2023-2026), Doctors for the Environment (Chair 2024-2026), Gastroenterological Society of Australia (GESA) Board (2025-2027). Editorial: UptoDate (Section Editor), Mayo Clinic Proceeding Associate Editor (2023-present). Financial support: Dr. Talley is supported by funding from the National Health and Medical Research Council (NHMRC) to the Centre for Research Excellence in Transforming Gut Health.

Funding

This research has been conducted with the support of the Australian Government Research Training Program Scholarship and the National Health and Medical Research Council (NHMRC) funded Centre of research Excellence in Transforming Gut Health. EH is supported by the Australian NSW Health Round 5 Early-Mid Career Grant.

Author contributions

EH and KD contributed to the design of this review and wrote the manuscript. The literature search and screening were conducted by EH, KD, NS, and GW; NT planned and supervised research, reviewed data analysis and the manuscript. All authors approved the final version of the manuscript for submission.

Acknowledgements

We are grateful for the support of Sophie Fowler, Katherine Barlow, and Benazir Carter in the assistance of screening the articles for this systematic review.

Data Availability Statement

All data referenced were obtained from the published sources cited in **Tables 1-3 and S3**. Data extractions were performed from associations reported in main texts, and supplementary data where available. As no re-analysis of raw data was conducted in this study, differences exist in processing pipelines and covariate use in analysis that were not controlled for.

References

1. Su D et al (2025) Projections for prevalence of Parkinson’s disease and its driving factors in 195 countries and territories to 2050: modelling study of Global Burden of Disease Study 2021. *BMJ* 388, e080952 https://doi.org:10.1136/bmj-2024-080952
2. de Lau LML, Breteler MMB (2006) Epidemiology of Parkinson's disease. Lancet Neurol 5:525–535. https://doi.org:10.1016/S1474-4422(06)70471-9
3. Houser MC, Tansey MG (2017) The gut-brain axis: is intestinal inflammation a silent driver of Parkinson’s disease pathogenesis? *npj Parkinson's Disease* 3 https://doi.org:10.1038/s41531-016-0002-0
4. Braak H et al (2003) Staging of brain pathology related to sporadic Parkinson’s disease. Neurobiol Aging 24:197–211. https://doi.org/10.1016/S0197-4580(02)00065-9. https://doi.org:
5. Hawkes CH, Del Tredici K, Braak H (2010) A timeline for Parkinson's disease. Parkinsonism Relat Disord 16:79–84. https://doi.org:10.1016/j.parkreldis.2009.08.007
6. Konings B et al (2023) Gastrointestinal syndromes preceding a diagnosis of Parkinson's disease: testing Braak's hypothesis using a nationwide database for comparison with Alzheimer's disease and cerebrovascular diseases. Gut 72:2103–2111. https://doi.org:10.1136/gutjnl-2023-329685
7. Drossman DA, Hasler WL, Rome IV-Functional GI (2016) Disorders: Disorders of Gut-Brain Interaction. Gastroenterology 150:1257–1261. https://doi.org:10.1053/j.gastro.2016.03.035
8. Sperber AD et al (2021) Worldwide Prevalence and Burden of Functional Gastrointestinal Disorders, Results of Rome Foundation Global Study. Gastroenterology 160:99–114e113. https://doi.org/10.1053/j.gastro.2020.04.014. https://doi.org:
9. Ford AC, Lacy BE, Talley NJ (2017) Irritable Bowel Syndrome. N Engl J Med 376:2566–2578. https://doi.org:10.1056/NEJMra1607547
10. Black CJ, Drossman DA, Talley NJ, Ruddy J, Ford AC (2020) Functional gastrointestinal disorders: advances in understanding and management. Lancet (London England) 396:1664–1674. https://doi.org:10.1016/s0140-6736(20)32115-2
11. Törnblom H et al (2026) Gastroduodenal Disorders Gastroenterology 170:1240–1260. https://doi.org:10.1053/j.gastro.2026.01.038
12. Pasricha PJ, Talley NJ (2026) Functional Dyspepsia. N Engl J Med 394:166–176. https://doi.org:10.1056/NEJMcp2501860
13. Enck P et al (2017) Functional dyspepsia. Nat Rev Dis Primers 3:17081. https://doi.org:10.1038/nrdp.2017.81
14. Fowler S, Hoedt EC, Talley NJ, Keely S, Burns GL (2022) Circadian Rhythms and Melatonin Metabolism in Patients With Disorders of Gut-Brain Interactions. Front Neurosci 16. https://doi.org:https://doi.org/10.3389/fnins.2022.825246
15. Ronkainen J et al (2021) Duodenal eosinophilia and the link to anxiety: A population-based endoscopic study. Neurogastroenterol Motil 33:e14109. https://doi.org:10.1111/nmo.14109

16. Warnecke T, Schäfer KH, Claus I, Del Tredici K, Jost WH (2022) Gastrointestinal involvement in Parkinson’s disease: pathophysiology, diagnosis, and management. npj Parkinson's Disease 8:31. https://doi.org:10.1038/s41531-022-00295-x
17. Chaudhuri KR, Schapira AH (2009) V. Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. Lancet Neurol 8:464–474. https://doi.org:10.1016/S1474-4422(09)70068-7
18. Su A, Gandhy R, Barlow C, Triadafilopoulos G (2017) A practical review of gastrointestinal manifestations in Parkinson's disease. Parkinsonism Relat Disord 39:17–26. https://doi.org:10.1016/j.parkreldis.2017.02.029
19. Xu J, Wang L, Chen X, Le W (2022) New Understanding on the Pathophysiology and Treatment of Constipation in Parkinson's Disease. Front Aging Neurosci 14:917499. https://doi.org:10.3389/fnagi.2022.917499
20. Choung RS et al (2016) Chronic constipation and co-morbidities: A prospective population-based nested case-control study. United Eur Gastroenterol J 4:142–151. https://doi.org:10.1177/2050640614558476
21. Camilleri M et al (2022) Oral ENT-01 targets enteric neurons to treat constipation in Parkinson disease: a randomized controlled trial. Ann Intern Med 175:1666–1674
22. Rusch C, Flanagan R, Suh H, Subramanian I (2023) To restrict or not to restrict? Practical considerations for optimizing dietary protein interactions on levodopa absorption in Parkinson’s disease. npj Parkinson's Disease 9:98. https://doi.org:10.1038/s41531-023-00541-w
23. Leta V et al (2023) Gastrointestinal barriers to levodopa transport and absorption in Parkinson's disease. Eur J Neurol 30:1465–1480. https://doi.org: https://doi.org/10.1111/ene.15734
24. Scheperjans F, Gut (2016) microbiota, 1013 new pieces in the Parkinson's disease puzzle. *Curr Opin Neurol* 29, 773–780 https://doi.org:10.1097/wco.0000000000000389
25. Scheperjans F et al (2015) Gut microbiota are related to Parkinson's disease and clinical phenotype. Mov Disord 30:350–358. https://doi.org:10.1002/mds.26069
26. Zhu M et al (2022) Gut Microbiota: A Novel Therapeutic Target for Parkinson's Disease. Front Immunol 13:937555. https://doi.org:10.3389/fimmu.2022.937555
27. Qian Y et al (2020) Gut metagenomics-derived genes as potential biomarkers of Parkinson’s disease. Brain 143:2474–2489. https://doi.org:10.1093/brain/awaa201
28. Chen J, Vitetta L (2020) The Role of Butyrate in Attenuating Pathobiont-Induced Hyperinflammation. Immune Netw 20:e15. https://doi.org:10.4110/in.2020.20.e15
29. Bedarf JR et al (2025) A prebiotic dietary pilot intervention restores faecal metabolites and may be neuroprotective in Parkinson’s Disease. npj Parkinson's Disease 11:66. https://doi.org:10.1038/s41531-025-00885-5
30. Krueger ME et al (2025) Comparative analysis of Parkinson’s and inflammatory bowel disease gut microbiomes reveals shared butyrate-producing bacteria depletion. npj Parkinson's Disease 11:50. https://doi.org:10.1038/s41531-025-00894-4

31. Liu SH et al (2025) Regulatory mechanisms of the gut microbiota-short chain fatty acids signaling axis in slow transit constipation and progress in multi-target interventions. Front Microbiol 16:1689597. https://doi.org:10.3389/fmicb.2025.1689597
32. Hoedt EC et al (2026) Shared functional microbiome signatures in Parkinson's disease and constipation predominate irritable bowel syndrome despite taxonomic divergence. *Brain, Behavior, & Immunity - Health* 53, 101218 https://doi.org:https://doi.org/10.1016/j.bbih.2026.101218
33. Lees A et al (2023) Optimizing levodopa therapy, when and how? Perspectives on the importance of delivery and the potential for an early combination approach. Expert Rev Neurother 23:15–24. https://doi.org:10.1080/14737175.2023.2176220
34. Duncanson K et al (2024) Diet-microbiota associations in gastrointestinal research: a systematic review. Gut Microbes 16:2350785. https://doi.org:10.1080/19490976.2024.2350785
35. Simm NM et al (2026) A Scoping Review of Methods Used to Investigate Relationships between Dietary Intake and the Gastrointestinal Microbiome. Nutr Rev nuaf306. https://doi.org:10.1093/nutrit/nuaf306
36. Tosefsky KN et al (2024) The Role of Diet in Parkinson's Disease. J Parkinsons Dis 14:S21–s34. https://doi.org:10.3233/jpd-230264
37. Cabanillas-Lazo M et al (2026) Probiotic, Prebiotic, or Synbiotic Supplementation in Parkinson's Disease: A Systematic Review and Meta-Analysis with Trial Sequential Analysis. Gerontology 72:126–141. https://doi.org:10.1159/000547665
38. Page MJ et al (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 372:71. https://doi.org:10.1136/bmj.n71
39. Yoon HJ et al (2024) Dietary quality and the gut microbiome in early-stage Parkinson's disease patients. Nutr Neurosci 27:761–769. https://doi.org:10.1080/1028415X.2023.2253025
40. Li C et al (2019) Gut Microbiota Differs Between Parkinson's Disease Patients and Healthy Controls in Northeast China. Front Mol Neurosci 12–2019. https://doi.org:10.3389/fnmol.2019.00171
41. Kwon D et al (2024) Diet and the gut microbiome in patients with Parkinson's disease. npj Parkinson's Disease 10:89. https://doi.org:10.1038/s41531-024-00681-7
42. García Milla P, Nieto Martínez G, Maulen M, Tapia C, Díaz W (2025) The effect of supplementation with prebiotic fiber on the gut microbiota of a group of older people with Parkinson's disease from the city of Santiago de Chile. A pilot study. Nutr Hosp 42:232–242. https://doi.org:10.20960/nh.05272
43. Forero-Rodríguez J et al (2024) Changes in Bacterial Gut Composition in Parkinson's Disease and Their Metabolic Contribution to Disease Development: A Gut Community Reconstruction Approach. Microorganisms 12:325
44. Chen CC et al (2025) Investigating Plasma Metabolomics and Gut Microbiota Changes Associated With Parkinson Disease: A Focus on Caffeine Metabolism. Neurology 104:e213592. https://doi.org:10.1212/wnl.0000000000213592

45. Becker A et al (2022) Effects of Resistant Starch on Symptoms, Fecal Markers, and Gut Microbiota in Parkinson's Disease — The RESISTA-PD Trial. Genom Proteom Bioinform 20:274–287. https://doi.org: https://doi.org/10.1016/j.gpb.2021.08.009
46. Hall DA et al (2023) An open label, non-randomized study assessing a prebiotic fiber intervention in a small cohort of Parkinson's disease participants. Nat Commun 14:926. https://doi.org:10.1038/s41467-023-36497-x
47. Meiners F, Ortega-Matienzo A, Fuellen G, Barrantes I (2025) Gut microbiome-mediated health effects of fiber and polyphenol-rich dietary interventions. Front Nutr 12:1647740. https://doi.org:10.3389/fnut.2025.1647740
48. McLoughlin RF, Berthon BS, Jensen ME, Baines KJ, Wood LG (2017) Short-chain fatty acids, prebiotics, synbiotics, and systemic inflammation: a systematic review and meta-analysis. Am J Clin Nutr 106:930–945. https://doi.org:10.3945/ajcn.117.156265
49. Notting F, Pirovano W, Sybesma W, Kort R (2023) The butyrate-producing and spore-forming bacterial genus Coprococcus as a potential biomarker for neurological disorders. Gut Microbiome (Camb) 4:e16. https://doi.org:10.1017/gmb.2023.14
50. Russo L et al (2015) Partially hydrolyzed guar gum in the treatment of irritable bowel syndrome with constipation: effects of gender, age, and body mass index. Saudi J Gastroenterol 21:104–110. https://doi.org:10.4103/1319-3767.153835
51. Wang Y et al (2023) Diet and gut microbial associations in irritable bowel syndrome according to disease subtype. Gut Microbes 15:2262130. https://doi.org:10.1080/19490976.2023.2262130
52. Motokawa S, Masuyama H (2023) Relationships between the proportion of dietary fiber intake and LPS biosynthesis pathway of human gut microbiota. J Japanese Soc Clin Stud Intestinal Microflora 25:30–37. https://doi.org:10.60353/jcsim.25.1_30

Tables

Table 1 to 3 are available in the Supplementary Files section.

Figures

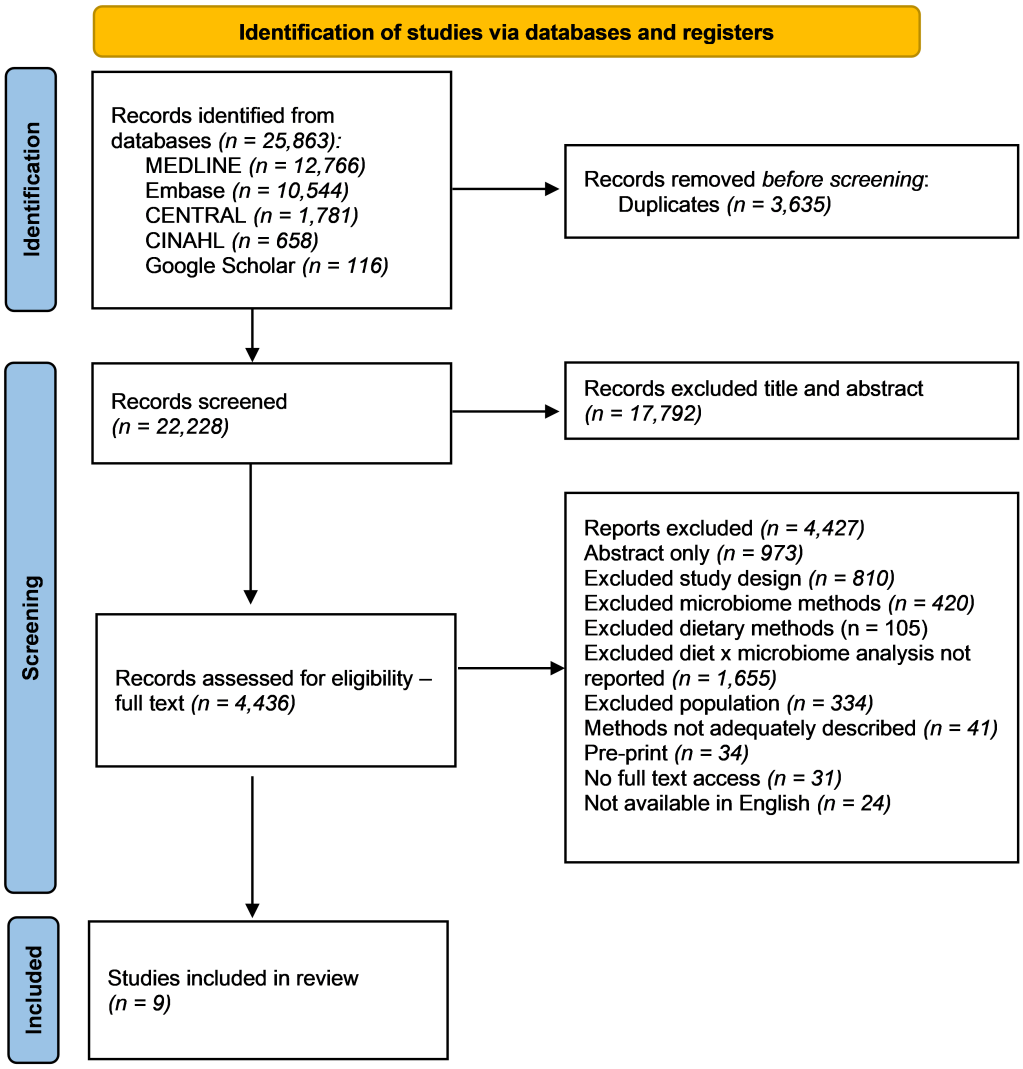


Figure 1

PRISMA Flow Diagram for the Identification and Selection of Studies

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarymaterial.docx
- Table13.docx